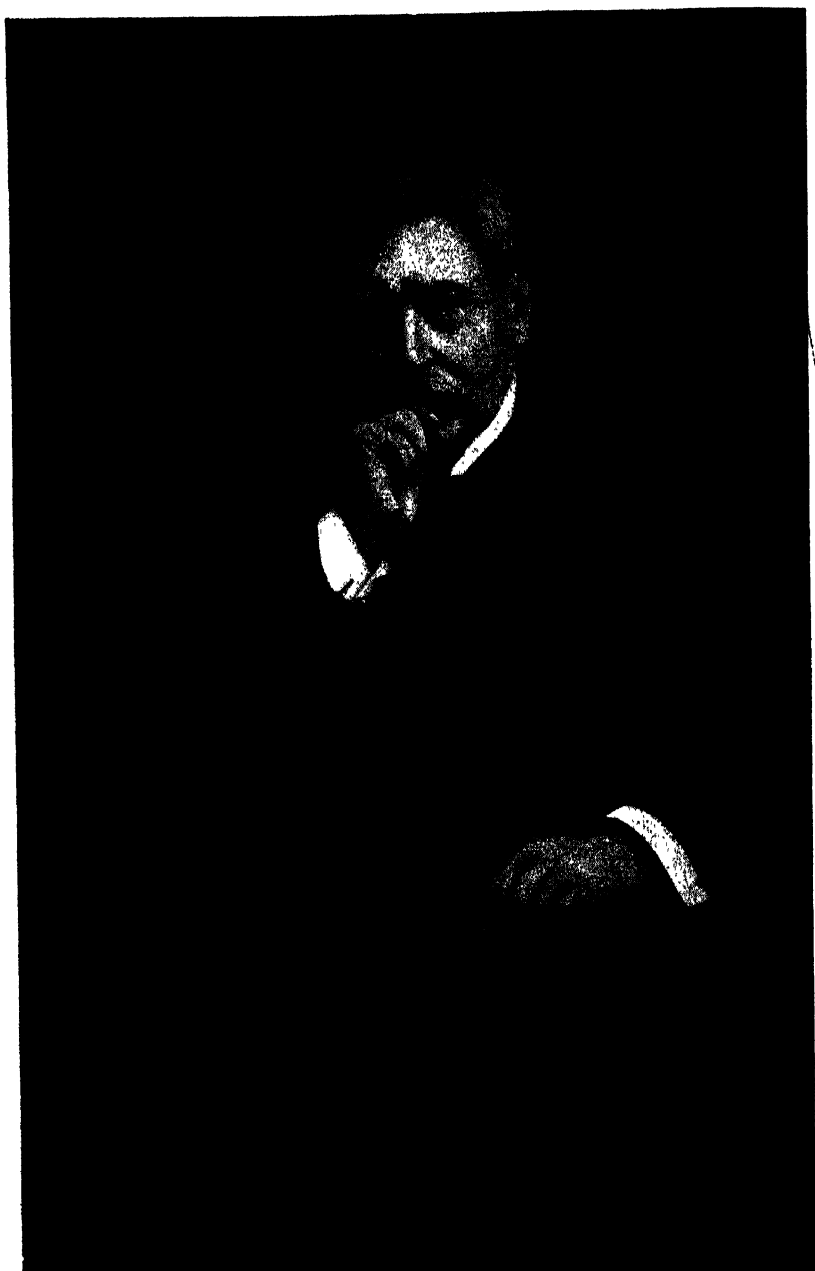


**MANSON'S
TROPICAL DISEASES**



SIR PATRICK MANSON, G.C.M.G., F.R.S.

PLATE I

MANSON'S TROPICAL DISEASES

A MANUAL OF THE DISEASES
OF WARM CLIMATES

EDITED BY
SIR PHILIP H. MANSON-BAHR

C.M.G., D.S.O., M.A., M.D. D.T.M. AND H. CANTAB.,
F.R.C.P. LOND., M.D. (Malaya-Hon. Causa).

Past President of the Royal Society of Tropical Medicine and Hygiene, London, and the Medical Society of London. Hon. Fellow Royal Soc. Med. Consulting Physician to the Hospital for Tropical Diseases, London; the Albert Dock Hospital and Tilbury Hospital. Consultant in Tropical Diseases to the Admiralty. Formerly lecturer on Tropical Medicine to King's College Hospital. Formerly Consulting Physician to the Colonial Office and Crown Agents for the Colonies. Formerly Consultant in Tropical Diseases to the Royal Air Force and Ministry of Pensions. Mary Kingsley Medal, Liverpool School of Tropical Medicine and Nocht Medal, Hamburg Tropeninstitut. Brumpt Prizeman, Paris. Late Director, Division of Tropical Medicine, London School of Hygiene and Tropical Medicine; and Lecturer on Tropical Medicine to the London Hospital; Associated Foreign Member of the Soci  t   de Pathologie Exotique and of the Soc. Belge de Med. Trop. Corresponding Member of the Netherlands Society of Tropical Medicine. Member of the Washington Academy of Medicine. Late Examiner in Tropical Medicine to the Conjoint Board of the Royal College of Physicians and Royal College of Surgeons, England, and to Cambridge and Hong Kong Universities. Author (with A. Alcock) of "The Life and Work of Sir Patrick Manson," 1927; "The Dysenteric Disorders," 1939, "Synopsis of Tropical Medicine," 1943; "History of the School of Tropical Medicine in London," 1956; "Patrick Manson", 1962.

CASSELL & COMPANY LTD

35 Red Lion Square, London, W.C.1

and at

MELBOURNE • SYDNEY • TORONTO • CAPE TOWN

JOHANNESBURG • AUCKLAND

First Published	1898
<i>Reprinted</i>	1954
<i>Reprinted</i>	1957
<i>Reprinted</i>	1960
<i>Reprinted</i>	1961
<i>Reprinted</i>	1964

PREFACE TO THE FIRST EDITION

A MANUAL on the diseases of warm climates, of handy size, and yet giving adequate information, has long been a want ; for the exigencies of travel and of tropical life are, as a rule, incompatible with big volumes and large libraries. This is the reason for the present work.

While it is hoped that the book may prove of practical service, it makes no pretension to being anything more than an introduction to the important department of medicine of which it treats ; in no sense is it put forward as a complete treatise, or as being in this respect comparable to the more elaborate works by Davidson, Scheube, Rho, Laveran, Corre, Roux, and other systematic writers in the same field.

The author avails himself of this opportunity to acknowledge the valuable assistance he has received, in revising the text, from Dr. L. Westenra Sambon and Mr. David Rees, M.R.C.S., L.R.C.P., Superintendent, London School of Tropical Medicine. He would also acknowledge his great obligation to Mr. Richard Muir, Pathological Laboratory, Edinburgh University, for his care and skill in preparing the illustrations.

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CHAPTER I

RESIDENCE IN THE TROPICS

PREPARATION FOR LIFE IN THE TROPICS

SINCE adequate supervision of the preparation, handling and storage of every article of food and drink is not possible at all times, all those who are proceeding to the tropics or sub-tropics, whenever they come into contact with native servants, and whenever they mix with the native population, or whenever they are forced to live in less sanitary surroundings than they have been accustomed to, should be inoculated about four weeks before departure against typhoid and paratyphoid (T.A.B.). Anticholera and antityphus inoculations may be necessary for those who are going out to the countries where these diseases are endemic. Very often vaccination against smallpox may not cause any obvious reaction, or in popular language, may not "take," but it must be attempted none the less. If for other reasons, such as business matters or preparing for departure, circumstances prevent this, both inoculation and vaccination can be given on board ship if the voyage is long enough, e.g., the journey to India. Allowance must be made for any possible reaction. Those proceeding to the West Coast or other parts of Africa, and to South America, where yellow fever is endemic, must be inoculated against this disease (*see* p. 337). It must be emphasized that out of the many thousands who have now been protected only a very few have contracted yellow fever, and it is now compulsory for all passengers flying to any part of Africa. The immunity produced lasts for six years. On account of the danger of encephalitic symptoms children under one year of age should not be inoculated against yellow fever.

T.A.B. inoculation should not be given to children under two years of age. It is usually quite unnecessary. The following procedure must be adopted:

1st day.—Anti-yellow fever inoculation (0·5 ml.).

2nd day.—T.A.B. inoculation (0·5 ml.), and if cholera mixed (0·5 ml.).

4th–5th day.—Vaccination against smallpox with vaccinia lymph.

9th–11th day.—Second T.A.B. inoculation (1 ml.) or if cholera is mixed (1 ml.).

(T.A.B. alone, first inoculation (0·5 ml.), the second (1 ml.), 9–11 days afterwards.) (Cholera alone—similar dosage and spacing.)

T.A.B. "booster" 0·5 ml. dose at yearly intervals.

International Certificates are essential for yellow fever, cholera and smallpox vaccination, but not for T.A.B. International Sanitary Regulations specify the following periods for the validity of International Certificates:

Smallpox.—Primary vaccination is valid for three years. Validity commences 8 days after vaccination. Revaccination is valid for three years. Validity commences at once.

Cholera.—Primary inoculation is valid for 6 months. Validity commences 6 days after inoculation. Re-inoculation is also valid for six months. Validity commences at once.

Yellow Fever.—Primary inoculation is valid for six years. Validity commences ten days after inoculation. Re-inoculation within six years. Valid for a further six years. Validity commences at once.

Generally, inoculation against yellow fever should be done first, and at least four days before a *primary* vaccination against smallpox. If a primary vaccination against smallpox is done first, there should be an interval of 21 days before yellow fever inoculation.

Active Immunization against Tetanus.—Immunity is conferred by the injection of tetanus toxoid (T.T.) and is now available combined with T.A.B. vaccine. For primary immunization against tetanus, 1·0 ml. of tetanus toxoid is injected subcutaneously: 1st injection 1·0 ml., 2nd injection 1·0 ml., not less than 6 nor more than 12 weeks after the first injection, 3rd injection 1·0 ml., 6–12 months after the second injection. These doses may be given to all persons of all ages and of either sex. The immunity conferred lasts for five years.

Active Immunization against Typhus Fever.—Typhus vaccine is prepared from suspensions of rickettsiæ grown in the yolk sac of developing chick embryos. The vaccine in present use is prepared at the Connaught Medical Laboratory, Toronto. These vaccines afford protection against louse-borne and flea-borne typhus. Primary immunization is obtained with three subcutaneous injections of 1·0 ml. of vaccine at weekly intervals. This dosage can be given to children, but infants under one year should not be immunized.

Reinforcement of Immunity.—A “booster” dose must be given every three months after primary immunization whilst the individual is at risk. Local discomfort at the site of inoculation is common. General reactions are rare. Active immunization against typhus fever is only used in the face of epidemics, its routine administration to those proceeding to the tropics is unjustified.

PATHOLOGICAL EFFECTS OF TROPICAL CLIMATE

Tropical heat produces in fair-skinned people a characteristic pallor, sometimes with a yellowish discolouration of the skin, which is to be distinguished from tropical anæmia. This appearance is due to blanching of the skin, from thickening of the surface layer and increased pigmentation.

The tropical light produces effects in the skin, which may be acute or chronic. They range from a slight sunburn to a severe erythema, accompanied by blisters and œdema, so that a reaction may set in produced by septic absorption. Sometimes this may be so severe as to produce delirium, or even coma. Chronic skin irritation is shown by pigmentation and by vasomotor changes; that this is a process of natural selection is demonstrated by the skin pigmentation of most native races, so that the nearer the equator, the darker the skin, whilst that of a European long resident in the tropics tends to darken. When slight pigmentation is established, probably as the result of increased blood supply, hair and nails grow more rapidly. Freckles—small brown pigmented macules—are specially apt to occur in sandy, red-haired, or fair children brought up in a tropical climate, and are often very disfiguring. Chronic solar dermatitis, or sailor's skin,

especially at the back of the neck or hands, is characterized by atrophy, wrinkling and pigmentation. White atrophic patches, telangiectases and warty growths (solar keratoses) develop: some of which, especially when situated on the dorsum of the hands, eventually become the seat of basal (rodent ulcer type) or squamous-celled neoplasms.

Summer eruption is a polymorphic eruption of erythema papules, vesicles, weeping areas, crusts, pigmented macules and small depressed scars, which occurs in exposed parts, especially among children. Johnson's Baby Powder is very useful.

Urticaria is occasionally produced by the actinic rays. *Xeroderma pigmentosum* (Kaposi's disease) is a congenital condition of light-sensitiveness, such as is produced by X-rays on a normal skin. This manifests itself by pigmentation, telangiectasis, keratoses, and finally epithelioma, and is produced by the ultra-violet region of the spectrum. It is said to be more frequent in the tropics than elsewhere. *Cheilitis actinica* is a condition of the lips caused by burning by ultra-violet light at high altitudes in S. Anatolia. Secondary carcinoma often results. *The effect of tropical sunlight on the eyes* is well known to produce glare conjunctivitis and chronic headache, necessitating smoked or tinted spectacles. Pterygium, or a triangular fibrous growth extending over the conjunctiva to the pupillary margin with its base towards one or other canthus, is common in tropical residents, and is considered to be a natural reaction to intense sunlight. (Edema of feet and legs in young adults is frequently noted on first entering a tropical climate. It is of peripheral vascular origin and is probably an indication of the adjustment of that system to new conditions. This oedema passes off on acclimatization.

The congestive disorders, affecting especially the liver and bowels, are probably due more to sudden changes of temperature. The concentration of the urine predisposes to gravel and probably accounts for the frequency of renal and vesical calculi in tropical residents, especially in hot dry climates, such as that of the plains of India and the arid districts of the Sudan and Northern Nigeria. People living in hot, dry climates with an inadequate water supply may suffer from backache or even renal colic, probably due to deposition of salts in the renal pelvis or ureter. It is evident that, where fluid loss is so great, exceptional intake of fluid becomes necessary.

INSECT BITES

Women are especially sensitive to mosquito bites, when they attack at sundown. Commonly they bite through mosquito netting when parts of the body are pressed against it during the night. Not all stinging insects convey disease and, of those that do, only a small proportion are infected with germs of tropical disease. There is some evidence that reactions to infective stings are the more painful. Stinging insects are more attracted to some individuals, especially those who are most sensitive. Some are shunned, possibly because of pigmentation of the skin or a deterrent odour.

In an African village it is a common sight to see Europeans being severely bitten, while the native children are undisturbed. There is no doubt that by constant exposure an immunity is gradually developed. There are others who become allergic which reveals itself by painful erythematous swellings, and in extreme cases in bullæ or blisters. Severe and fatal anaphylaxis may occur, as in the case of bees' and wasps' stings (*see p. 678*).

Complications are due to septic infections. Mellanby has shown that, in scabies, excessive irritation is due to faecal secretion and secondary infection. The nature of the protein injected varies with the type of insect, and the subsequent reaction is highly specific. Some people are sensitive to *Aedes*, but not to *Culex* or *Anopheles*.

A relatively small number of mosquitoes inject a substance of a toxic nature that causes a delayed reaction and renders the lesion liable to reappear during the night. The salivary secretions contain anti-coagulants, red-cell agglutinins and hæmolysins.

In the case of the reduviids, vectors of *Trypanosoma cruzi*, only a small proportion are sensitive to their bites, and it appears probable that these insensitized persons are less liable to contract this infection.

The bite of the tsetse is rapid, sharp and painful, but it is seldom followed by any reaction, unless infected. The proboscis is a rigid structure and is inserted to an increasing depth until it encounters a blood vessel from which the insect feeds. With the proboscis of the mosquito the tissues are probed in all directions, producing laceration.

Most insects select different parts of the body for their attacks. Mosquitoes, diurnal or nocturnal, are attracted to the most vascular parts, wrists, forearms or ankles.

Usually the bites produce small raised erythematous areas, but on the face a generalized oedema sometimes ensues.

Midges (*Ceratopogonidæ*) are crepuscular, attacking the face and other exposed parts producing small vesicles.

Fleas usually bite around the neck and waist, producing small, linear and often hæmorrhagic, vesicles. The irritation is probably caused by defæcation of the insect into the wound.

Bugs (*Hemiptera*) usually attack the face of the victim when asleep, especially round the orbits which become oedematous.

Lice (*Anoplura*) usually bite around the waist-line, causing hæmorrhagic lesions which often run in a linear direction.

Crab lice (*Phthirus*) are usually confined to the hairs of the pubic region, but may invade the hairy skin from the knees to the eyebrows.

Horse flies—*Tabanidæ*, *Chrysops* and *Hematopota*—usually cause painful bites, attacking any exposed areas.

Mites (*Trombiculæ*), which transmit scrub typhus, burrow beneath the skin, producing small vesicular, and extremely painful, lesions. When infected with rickettsiæ the site becomes gangrenous and a primary sore, or *eschar*, ensues.

Ticks cause painful, localized swellings which may become necrotic. The feet and legs are usually attacked first, though they may attach themselves to any part. The lesions are due to the insertion of the head (*capitulum*) into the skin.

Treatment.—Local application of antihistamine creams to bee or wasp stings is useless, but Prime (1958) has found that taking 0.5 mgm. diphenylpyratine (Histryl spansule) about half-an-hour before opening bee-hives, prevents all unpleasant after effects.

Irritation and itching can be relieved by the application of Scrubb's ammonia, tincture of iodine, Reckitt's blue, but, under modern conditions, by antihistamine preparations—a number of which are now procurable. A good antidote is *Thephorin* ointment (Roche). This contains 5 per cent. of active substances in a simple water-miscible base of polyethylene glycols. It should be applied to and rubbed into the site of the bite, or bites, at frequent intervals. *Thephorin* is phenyl-methyl-tetrahydroaza-fluorine hydrogen tartrate. 1 per cent. menthol in 95 per cent. alcohol is useful.

CHAPTER II

GENERAL DISEASES OCCURRING IN THE TROPICS

DISEASES OF THE DIGESTIVE SYSTEM

LITTLE is known about variations in gastric secretion in the tropics, save that in ancylostomiasis and other worm infestations the secretion of hydrochloric acid by the oxyntic cells is reduced ; but it is a striking fact that gastric and duodenal ulcers are seldom encountered in native races living on a simple carbohydrate diet. This applies especially to Indians, Indonesians and Negroes. As the result of 2,170 autopsies, Kouwenaar, in Indonesia, concluded that ulcers of the stomach and duodenum are found only in 1 per cent. of Indonesians as against 10 per cent. of Chinese, but they are said to be very common in Abyssinians, and this fact is ascribed to dietetic causes (Bergsma). Wanless finds them common in rural districts of western India, due to septic mouths and excessive stimulation by hot curries. Miles (1958) has found in the West Indies that peptic ulceration is common enough, but rarely produces hæmorrhage, but the tendency of ulceration is towards stenosis and fibrosis of duodenal ulcers which in turn is due to a fibroplastic diathesis. Diverticulosis and diverticulitis appear to be very rare or almost unknown.

Acute intestinal obstruction has a high incidence. It is often due to food—especially mangoes (the stones or swollen fibrous contents). It may be due to lymphogranuloma of rectum also. Volvulus of the small bowel in children may be due to matted coils of ascaris, to polypi or Meckel's diverticulum. Strangulated herniæ of all types are common, umbilical especially.

APPENDICITIS

Inflammation of the appendix is rare, and fulminating cases requiring immediate operation seldom occur in native races, in marked contrast to the frequency of this condition in European residents. In Indians, both Moslems and Hindoos, acute appendicitis is extremely rare and the Editor has seen only two cases in over forty years.

With the advance of civilization it has been noted in the Belgian Congo and in the West Indies that acute cases of appendicitis are becoming more common in larger centres. In the tropics inflammation of the appendix may ensue in amœbic dysentery, schistosomiasis, paragonimiasis, leptospirosis, enteric fever, relapsing fever, widow spider poisoning, bubonic plague, subtertian malaria, with intestinal worms, such as *Tænia saginata*, *Ascaris lumbricoides*, and *Enterobius vermicularis*.

Possibly the lower incidence in the European is due to diet. Miles (1958) warns that in the West Indian Negroes gonococcal salpingitis is alarmingly prevalent and presents a problem of differential diagnosis of some importance. Ectopic gestation, due to the same infection of the Fallopian tubes, is another complication. Right sided pain is associated with irregular menstruation.

DISEASES OCCURRING IN THE TROPICS

CARCINOMA OF THE STOMACH AND INTESTINAL TRACT

The rarity of malignant growths in the alimentary tract in native races has been the subject of much speculation. De Langen has laid special stress on the fact that gastric carcinoma is noticeably absent among the Javanese. The same is true in India and, as far as can be ascertained, in Central Africa. The comparatively short life-span of natives, in contrast to that of Europeans, may account for this difference.

CIRRHOSIS OF THE LIVER AND SPLENIC ABSCESS

All writers on tropical pathology have laid stress on the frequency of liver cirrhosis with ascites among native races, where the influence of alcohol can be discounted. Excluding cases caused by parasitic infection, there remains a residue, of unknown ætiology, resembling the cirrhosis of Lænec. There are now cogent reasons for believing that it is the result of chronic malnutrition which is accompanied by fatty infiltration of the liver and changes in the pancreas (Gillman and Davies, 1948) (*see* page 420). Walters and Waterlow (1954), in the Gambia, suggested that the prevalent type of portal fibrosis had a dual ætiology, in that minimal malnutritional damage to liver cells was sufficient to stimulate a fibrosis when the stromal tissues of the liver had become sensitized, by over-reaction through the macro-molecular bombardment of malarial pigment. Hypoprotinæmia is invariable, and there is inversion of the albumin-globulin ratio. The serum therefore gives a positive globin test (*see* p. 149) and differential diagnosis has to be made from tuberculous peritonitis, adherent pericardium and kala-azar.

Banti's syndrome with splenomegaly, anæmia, leucopenia and thrombocytopenia, with varying degrees of liver cirrhosis, is also met, especially in China.

Primary Abscess of the Spleen, which is very common in Rhodesia, was first described by Wallace at Broken Hill (Rhodesia) in 1922. He concluded that the abscess was caused by thrombosis of the splenic vein leading to a highly active necrosis of that organ when it had become secondarily infected. A tumour over the splenic area which is tympanitic is of itself suggestive. It is usually met in young adults. It starts abruptly with fever and pain in the left hypochondrium. This swelling rapidly enlarges upwards and downwards, thus raising the left dome of the diaphragm. When a splenic tumour is present a tympanitic note is very suspicious.

Diagnostic aspiration must be performed without delay. The aspirated pus is fluid, of a reddish colour, often frothy and sterile on culture, and has to be distinguished from amœbic and spirochaetal abscesses (*see* p. 174).

DISEASES OF THE GALL-BLADDER

The rarity of cholecystitis in native races is striking. As the Editor has pointed out, there appears to be no direct connection between dysenteric infection and inflammation of the gall-bladder, nor is there any predisposition to cholelithiasis. De Langen and Lichtenstein report that among 150,000 out-patients in Jakarta they were only able to make a

diagnosis of gall-stones once, and among 422,948 other patients thirty times. Intrahepatic cholesterin stones, however, appear to be not infrequent. In West Africans cholecystitis is apt to coincide with a "sickling" crisis.

DISEASES OF THE HEART, LIVER, BLOOD-VESSELS AND PORPHYRIA

Valvular heart disease in the tropics is usually syphilitic. Williams (1938) in Uganda found that syphilis accounted for 53 out of 94 cases of heart disease and that "syphilitic" heart is five times as frequent as any other cardiac condition; aortic syphilis (aortic regurgitation) was found in 86 out of 894 post-mortem examinations. The average age of onset of symptoms in natives is forty-one years, i.e., considerably earlier than in Europeans. Macfie and Ingram (1920) found cardiac aneurysm very frequent on the Gold Coast. Aneurysms, often multiple, are extremely common in the Chinese, and rupture is one of the most frequent causes of sudden death.

Rheumatic valvular disease is a subject upon which much more precise information is required. There is some evidence (*see* p. 12), that rheumatic infection does occur. Chesterman has seen typical rheumatic hearts at autopsy on the Congo. Barnes has found rheumatic carditis with valvular disease comparatively common in Fijians. Davies in Uganda, in a series of 2,994 autopsies, reported evidence of rheumatic carditis only in 22 cases: mitral stenosis in 21, acute bacterial endocarditis, on the other hand, was present in 2.5 per cent. of all autopsies. Acute rheumatic carditis, in all its forms, is however extremely prevalent in the Asian population of Durban (Cosnett, 1957). Sclerosis of the coronary vessels appears in normal frequency with advancing age, as in Europeans, but it is a curious fact that the clinical syndrome of angina pectoris is usually absent. Hyman (1946) found arteriosclerosis to be unduly common in Melanesians. Most were too old at fifty and many of thirty years had tortuous arteries. Blood-pressure readings as high as 230 systolic and 115 diastolic were recorded. Pulmonary and apical systolic murmurs are common in these peoples. Davies in Uganda has found that hypertensive renal disease accounted for 81 per cent. of all cardio-vascular conditions and was commonest between the ages of twenty and thirty. Hyperpiesia appears to be practically absent in poorer natives living on a carbohydrate dietary, though Wilkinson found it common in South China, tending to increase with westernization of habits. It should be observed that the normal blood-pressure, systolic and diastolic, in natives in the tropics, owing to smaller intake of protein, is 10-15 mm. of mercury lower than the normal in Europe. In those suffering from subnutrition, it is lower still. Under the heading of "endocardial fibrosis"—a form of heart disease which is peculiar to the tropics—has been discussed by Gray (1951). First described by Josserrand and Gallavardin (1901), a series of 40 cases of unexplained heart failure in African troops was investigated by Bedford and Konstam in 1946. Davies has found it in 86 out of 3,759 necropsies in Uganda; Edge one in a European in W. Africa, and Gray two others in Europeans in Nigeria. Clinically this condition reveals itself as congestive heart failure of insidious onset in young adults. The main features are cardiac

enlargement, low blood-pressure and sinus arrhythmia. Electrocardiograms show low-voltage curves with inversion or flattening of the "T" wave. Embolic phenomena and opaque endocardium with fibrous tissue extending into the endocardial myocardium and mural thrombosis are almost always present. The apical portions of the ventricles are most commonly involved. Williams, Ball and Davies (1954) have described four clinical patterns. In the first the left ventricle is mainly affected and the result is simple bilateral heart failure; in the second there is obliterative fibrosis of the right ventricle, producing right-heart failure; in the third the posterior cusp of the mitral valve is adherent to the ventricle producing mitral incompetence; in the fourth there is bicuspid incompetence produced by adhesions of the posterior cusp of this valve to the ventricle. There is evidence of injury and fibrosis due to the action of some toxin. Fibrillation does not occur and blood-pressure remains low.

Fawdry (1955) has described *hepatomegaly*, associated with *splenomegaly* and refractory anaemia in S. Yemen and the Aden Protectorate. In some the enlargement of the liver is confined to the *left lobe*. In some districts 60 per cent. of Arabs have large spleens. In liver biopsies a wide range of fibrosis is demonstrated. The anaemia is microcytic or hypochromic with leucopenia of 4,000. There is no significant rise in plasma proteins and globulin values are high. Clinton Manson-Bahr has recognized a similar disease in the Kavirondo tribes round L. Victoria and in the Wakamba E. of Mount Kenya, but not in the Kikuyu. Zlotnick (1955) in Jerusalem has described peculiar oval parasites within the monocytes at autopsy in a similar condition.

Acute thrombophlebitis, originally described by Gelfand in Northern Rhodesia, assumed epidemic proportions in East Africa during 1943-44. Thrombophlebitis is accompanied by pyrexia of a relapsing character, sometimes associated with stiff neck. Three varieties of this syndrome have been described: (1) a short-term fever with stiff neck often followed by relapses, (2) thrombophlebitis affecting one or more limbs, (3) pyrexia without evident phlebitis. Most of the cases had been subjected to venipuncture and there is some evidence that the primary cause may be a virus possibly transmitted by syringes (C. Manson-Bahr and Charters). This suggestion has received some support from pathological studies which reveal proliferation of young capillaries and the presence of phloxophil intracytoplasmic inclusions. It differs from thrombophlebitis migrans in running a shorter course and by being dissociated with thrombosis of the pulmonary vein or with thromboangitis obliterans (Bürger's disease) which is especially common amongst the Southern Chinese. Gelfand (1947) has described symmetrical gangrene of the feet occurring in Africans from Mashonaland preceded by pain and oedema. It was seen only in males between twenty and thirty-five years. The gangrene occurred simultaneously on both sides. In four cases it was limited to the tips and pads of all the digits, but in one the whole of both feet up to 8 ins. above the ankle-joint was affected.

Familial Porphyria occurs as a familial disorder in Europeans in S. Africa. It has a non-sex linked Mendelian dominant characteristic and all are descendants of one forebear. It causes no symptoms in childhood

and even in adults they are mild. The exposed skin blisters easily and scratching the back of the hand leaves a scar. Women frequently complain of abdominal pain, especially during pregnancy. Attacks are precipitated by drugs and alcohol. Porphyrria may be detected by careful spectroscopic examination of urine, but more precise information is obtained by quantitative examination for faecal porphyrria. In the acute stage the urine may be reddish-brown, darkening on standing and with ultraviolet light there is marked red fluorescence. Gelfand and Mitchell (1957) find that it is common in the Bantu in S. Rhodesia and resembles the form previously described by Barnes (1945 and 1955) in the indigenous population of the Witwatersrand. In the European this porphyrria has not the benign nature of the disease in the Bantu, which is of the delayed or cutaneous type. The disease is recognized by blistering of the parts exposed to the sun, by a darkening of the face and hands with nail dystrophies. The urine is of a Burgundy red, pink, or sherry in colour, containing porphyrins and an abnormal amount of urobilin. There is usually hypertrichosis, limited to the pre-auricular and temporal regions. In half there is hepatomegaly. This condition is commonest in the third and fourth decades. More males appear to be affected than females. It appears to be rare in native reserves and to be in some way connected with the drinking of "skokiaan," a potent African drink.

DISEASES OF THE KIDNEY AND GENITO-URINARY TRACT

Vesical and *renal calculi* are amongst the most common conditions encountered in the tropics, the former being the more frequent, especially among boys and young men. Little is known of their exact causation. By some the explanation is thought to lie in the high concentration of the urine: by others in an unbalanced dietary with lack of vitamin A. Urinary calculi are specially common in South China. Where urinary schistosomiasis is common (Africa), the eggs of *Schistosoma haematobium* frequently form the nuclei of calculi.

Acute nephritis (acute glomerulonephritis) is commonly encountered, and is attributed to septic intoxication. De Langen and Wilkinson remark upon its frequency, especially in conjunction with scabies and with super-added septic infections. The clinical picture of contracted kidney with accompanying cardiac hypertrophy and hyperpiesia is rarely seen in indigenous natives, but in those who have adopted European habits, and in Chinese and Europeans in the tropics, it appears to be as common as elsewhere. The rarity of granular kidney is possibly correlated with the simpler diet and its low protein content. Chronic nephritis is especially common in South China.

The clinical picture of *nephrosis* (F. von Müller) is frequently seen. This is characterized by extensive and widespread oedema, and a high, but usually variable, albuminuria. There is a low total protein in the blood, and an inverted albumin-globulin ratio with increased cholesterolæmia. The urea and residual nitrogen are unchanged, whilst the blood-pressure remains normal without effect upon the heart. Nephrosis has often a syphilitic basis, and may be seen together with *quartan* malaria (see pp. 49,

50). When all the causes are considered, there still remains a considerable proportion of cases without ascertainable ætiological basis, though many are found in association with ancylostomiasis.

Gonorrhæa, with its accompaniments, is one of the most common and widespread infections throughout the tropics. No one can estimate the extent of its prevalence or the disability that it causes. Not only is it responsible for joint and eye affections, but also for much serious disease of the female genitalia. Blacklock, in a thorough medical survey of Sierra Leone in 1930, estimated that 50 per cent. of males over fourteen had active signs and symptoms of this infection.

Epidemic epididymo-orchitis occurs in Malta and resembles the non-specific form described in England (Ainsworth-Davis). The fever which accompanies it occurs in two phases, a prodromal, followed by testicular fever, lasting four days. The testicular swelling subsides during the first week and resolves within a month. Atrophy occurs rarely.

DIABETES AND GLYCOSURIA

It has long been believed that true diabetes (*diabetes mellitus*) is very common in all parts of the tropics. This is possibly due to a high consumption of carbohydrates. The fact is that sugar (or substances which reduce Fehling's and Benedict's reagents) is comparatively often found in the urine amongst the Europeans and better-class natives in the tropics, but seldom in natives of the poorer class. De Langen, for instance, states that the incidence of diabetes in Indonesians is about 1 in 11,000, i.e., less than 0·01 per cent.

In India and Pakistan, diabetes is found among the richer people. Its comparative rarity in poorer natives is possibly to be ascribed to their shorter expectation of life. Diabetes usually develops in patients of riper years—those over fifty—and this factor may play a considerable part in statistical records. The relationship between obesity and diabetes is probably also important. Obesity is seldom seen in the average native, but among the rich, who can indulge more freely at table, a relatively higher incidence is observed.

The large number of cases of *benign glycosuria* in the tropics is remarkable, and these include the condition known as "renal diabetes." In this condition the blood-sugar content should not rise above normal. Patients with benign glycosuria feel perfectly well and show none of the usual symptoms of diabetes. The outlook in renal diabetes is favourable and the expectation of life is not affected.

Hæmosiderosis has been found to be common in the Bantu by Gelfand by employing the Prussian blue, or Perl reaction, by the addition of HCl and potassium ferrocyanide which in the presence of free iron gives blue ferric ferrocyanide. In this condition ten times the normal are found in the spleen, liver, thyroid, heart and pancreas. The blood contains normal or subnormal amounts of iron. It differs from ordinary hæmochromatosis because the iron-containing pigment is differently located suggesting storage in the liver and reticulo-endothelium and the urine is sugar-free. In siderosis there are massive amounts in the jejunum and duodenal

mucosa. During the course of 105 autopsies—75 adults and 30 children in Salisbury—68 per cent. of adults and 18 per cent. of children had siderosis. Although there is no evidence of any pathological effects it is accepted that siderosis is common in Central Africa. The total blood iron is increased, though not to the extent seen in idiopathic hæmochromatosis. The condition is attributed to excessive iron intake from iron cooking pots and also to protein deficiency.

GENERAL DISEASES

Gout.—It has always been held that there is a close connection between gout, obesity and overeating. It is also agreed that during the last half-century the incidence of this disease has almost everywhere decreased. It is always assumed that gout is very rare, or indeed non-existent, among tropical natives. Certainly it is seldom, if ever, observed in primitive peoples, and then only in those who have adopted European habits and customs. The Mahommedans suffer occasionally, while the Hindoos are said to escape entirely. In Manson's time gout was very rare in China, and in his diary he recorded one instance of gouty concretions in a Chinaman as an event of great importance. De Langen states that it has occasionally been observed in Java and the East Indies, but records in British India and in Central Africa are quite exceptional. Gout is said to be unknown in Egypt and in all the countries along the northern shores of Africa.

Endemic Fluorosis, with characteristic mottled dental enamel and spondylitis, occurs in its extreme form in some parts of India (Madras Presidency; Shortt and McRobert, 1937); in Kweichow, at the northern tip of Yunnan, China and especially on the shores of the Persian Gulf. It is due to drinking water containing fluorine.

Rickets—"Youbas" (Ghana).—Jelliffe (1951) has stated that, though rickets has been generally considered to be a rare disease in the tropics, it is found in West African children in Ghana. This form is of a mild type and is ascribed to deficient maternal diet, to prematurity and insufficient exposure to ultra-violet light.

The dietary deficiency is due to prolonged breast feeding and weaning on a diet consisting mostly of carbohydrates with a complete lack of Vitamin D. The deficiency is accentuated by interference of calcium produced by phytic acid, which is present in maize (as in the maize paste known as "pap"). In children under two the anterior fontanelle is widely open with a soft spongy edge. There is gross *caput quadratum* and bossing of skull with classical "hot cross bun" (*caput natiforme*) appearance.

Arthritis.—Arthritis, including the infective and rheumatoid forms, occurs in native races, but to nothing like the same extent as in Europeans in temperate climates. Exact figures are very difficult to procure, as it is necessarily very difficult to exclude gonorrhœal arthritis. The available information has been included by McKinley in a table which purports to give the relative figures of incidence in various tropical and subtropical countries, but it is doubtful if the figures can be considered really reliable.

In Ceylon, for instance, the number reported annually is given as 4,029, and the figure of 2,328 for the whole of India can hardly be considered accurate.

Dowling (1946) has described in Northern Australia a form of epidemic polyarthritis not reported elsewhere. It occurred in outbreaks of short, mild fever accompanied by polyarthritis, by pain and stiffness of several joints, especially those of hands and feet. Occasionally the knee joint is affected. The periarticular swellings persisted for 4-9 days. In the majority there was a papular or macular rash on the seventh day, occurring on the trunk and limbs and lasting 2-7 days.

This disease has recently become prominent in the Upper Murray Valley of South Australia. It is thought to be of viral aetiology and probably arthropod-transmitted. It occurs in river valleys in seasons of flooding (Fuller and Warner, 1957).

Acute articular rheumatism.—This apparently exists all over the world, but infrequently in native races, especially where the climate is hot and dry; consequently, the incidence of rheumatic valvular disease of the heart is correspondingly rare. Acute rheumatism with carditis and chorea are excessively common in the Asian population of Durban and are very severe. Rheumatic carditis provides the commonest cause of death in the 10-20 age group in the Asian population of this city (Cosnett, 1957). Mackinnon states that chorea is never seen in East African children. Fernando, in Ceylon, however, from extensive clinical and pathological observations, found that rheumatic infection is an important cause of carditis and accounts for one-quarter of the total number of cardiac cases. Wilkinson has testified to its presence in South China. On the other hand, Chesterman on the Congo found it very rarely in the native population, but it has been recognized in African children in Ghana and in Nigeria, where it occasionally leads to mitral stenosis. Although acute rheumatism has been noted with normal frequency in European residents it is difficult to obtain more accurate information from the meagre data available.

Tietze's Disease.—The occurrence of painless almond-shaped swellings of the costochondral junctions with stretching of the skin, without suppuration, but which is very painful on moving or twisting the trunk has been reported by Browne (1956) on the Congo. These fusiform swellings usually last 4-5 days. The disease was originally described by Tietze in 1921.

DISEASES OF THE RESPIRATORY SYSTEM

Tuberculosis.—It has gradually been recognized that the extent of tuberculosis in the tropics is much greater than was formerly thought possible. The rapidity of spread and malignancy of course of pulmonary tuberculosis when first introduced into the Pacific Islands have been fully realized, and are well described by Robert Louis Stevenson among the Marquesans. Similar disasters have occurred in Fiji, Samoa, Tonga and other Pacific Islands. In India, Rogers (1919) found no less than 9 per cent. of deaths due to tuberculosis, and Megaw estimated that, in the whole country, two million people are suffering from it. Scott has drawn attention to the pathological peculiarities of tuberculosis in Southern China. It has proved to be one of the main causes of death in Jamaica,

Ghana, the Philippines, on the Congo, and in Tanganyika, where it has been studied by Wilcocks.

For the rapid spread of the disease, its virulent nature, and the poor resistance offered by primitive peoples, several factors are responsible. Usually the patients do not come for medical treatment until they are in an advanced stage. The sputum is loaded with bacilli and, living as they do in primitive huts or houses crowded together, infected natives are a constant source of danger to their fellows. Spitting is a universal habit, and undernutrition and co-existing malarial and parasitic infections render them all the more susceptible.

The most important factor in the epidemiology of tropical tuberculosis is contact. Natives are able to resist a first infection but, once the disease has become established, their resistance is low. During the last twelve years there has been an enormous increase in reported cases; in some instances, as in Nigeria and British Guiana, it has been five- and six-fold, especially in the mining areas.

Unfortunately, tuberculosis is a disease which spreads with civilization, e.g., it was unknown many years ago in the Cameroons and in the southern Sudan. In Hong Kong, Scott, in an average of 4,000 autopsies a year, found marked tuberculosis in 5 per cent., and of these, three-fourths were children under ten. Tuberculosis among natives may be divided into two types, viz., "*natural*" tuberculosis, characteristic of those not immunized in any way against the disease, as in laboratory animals; and "*modified*" tuberculosis, a more chronic condition, so called because it is modified by primary infection.

It appears to be generally agreed that hæmoptysis is not a prominent sign of tuberculosis in native children, though extraordinarily frequent in adults. Scott asserted that, however extensive the disease, however large the cavity, he had never seen fatal hæmorrhage in a child. Spontaneous pneumothorax is found, but amyloid disease in chronic cases is very rare. Bovine tuberculosis, though it occurs, does not appear to be common.

Intestinal tuberculosis and tuberculous peritonitis are especially prevalent in China, and bone tuberculosis in West Africa. Recent writers have all stressed the importance of the nutritional basis as a factor of the first magnitude in the spread of tuberculosis in native populations. Both pulmonary and bone tuberculosis are rife among the Bedouin population of Arabia.

Pneumonia.—Pneumonia, a principal cause of death almost everywhere in the tropics, especially in those countries with a persisting high humid atmosphere, has one of the highest mortality figures. Epidemics are specially found where native labourers are gathered together in compounds and in mining camps. The cause of the disease is usually a pneumococcal septicæmia, with little localization in the lungs. The clinical picture—rapid onset, extreme prostration and absence of the sthenic signs and symptoms which characterize the disease in Europeans, and of a termination by crisis—differs very considerably from that seen in temperate zones. All these factors impart a varying clinical picture and confound the newly-arrived doctor in the tropics. The story of pneumonia and its ravages in the Rand Mines and in the copper belt of Northern Rhodesia

is familiar to students of this subject. It is in the treatment of pneumonia in tropical natives that sulphonamides and penicillin appear to be having their greatest triumphs.

Syphilis of the lung is not uncommon in Bantus in South Africa and also in Indians (Walters). The lesions take the form of gummata or diffuse fibrosis. The signs and symptoms may resemble those of tuberculosis (Dormer and colleagues, 1945).

ZYMOTIC DISEASES

Scarlet fever (scarlatina).—All observers agree that scarlet fever either is never seen in the tropics, or is very rare. De Langen, in the Dutch East Indies, asserts that such cases as have been tentatively diagnosed eventually prove to be something else. Fischer and others who have looked for it amongst the negroes of Central Africa have never found it. Probably the disease exists on the Gold Coast and Nigeria in such a mild state as to be unrecognizable, and the rash may be almost invisible on a dark skin (Gillespie).

Application of the Dick test to a selected number of tribes in Tanganyika showed a certain percentage of positive reactions, equal only to about one-third of the figure usually observed in Europeans; the few cases reported from Central Africa have all been among European residents. Böttcher (1934) has compiled a review of this subject. In South America and the West Indies, on the other hand, the disease occurs in sporadic outbreaks. In India, too, it is known, though rare; it is of a mild type and specially apt to attack small children. According to Megaw and das Gupta, from 1923 to 1926 scarlet fever was reported from 212 districts, but nearly all cases were European residents. It is common in North China, though it does not occur in the south. Jensen (1940) states that in China and the Pacific Islands scarlet fever is newly imported, and that the nearer to the equator the less is the morbidity and mortality. Zöller (1925) found that the Dick test gave uniformly negative results.

Measles.—Measles is widespread throughout all tropical countries and runs the same course as elsewhere, and the malignant type is not uncommon. Where no inherent immunity towards the virus exists, as in the Pacific Islands (especially Fiji and Rotumah), a measles epidemic may cause a high mortality in adults as well as children; thus in 1874 over 25,000 Fijians died from this disease. The measles rash has to be distinguished from that of typhus and dengue, but its appearance, though modified by a dark skin, is quite characteristic.

Diphtheria.—Diphtheria appears to be widespread and occurs in epidemic form, often when least expected. It is a disease of civilization and is evident only in towns and centres of population. It is recorded in the epidemiological statistics of most countries, with the exception of Africa. Whereas it is common in the northern and southern subtropical portions, it is apparently very rare in the tropical zone, and even at the present day in East Africa, Uganda, Tanganyika and in West Africa, only sporadic cases are discovered. Cutaneous diphtheria, implanted on desert sores, was commonly observed among troops of all races fighting in the Middle East in World Wars I and II (see p. 650).

Mumps.—In the tropics this may be a generalized disease and assume a malignant form. In one-third of the cases orchitis is a complication. It is stated that the virus attacks the central nervous system, causing changes in the cerebrospinal fluid. Patients suffer from hallucinations and delirium—sometimes also they show Kernig's sign, bradycardia and ocular symptoms.

Bornholm disease, or epidemic pleurodynia, has been found in widespread epidemics in the Tonga and Cook Islands in the Pacific and in E. Africa. The Europeans suffered equally with the native population (Matheson). An extensive outbreak has been reported by Jamieson and Prinsley from Aden in 1947. It is also known as the "devil's grip" or "epidemic myalgia." A number of cases of meningo-encephalitis have been recorded (1957) in S. Rhodesia during a mild epidemic of this disease. Five had slight stiff neck rigidity with normal C.S.F. The virus (Coxsackie virus of four types) occurs in the faeces and is diagnosed by the paralysis it produces in baby mice, as a result of widespread and acute necrosis of skeletal muscles.

DISEASES OF THE CENTRAL NERVOUS SYSTEM

Syphilitic diseases of the central nervous system, such as tabes and general paresis, are seldom observed in Central Africa and the Pacific Islands, and this observation has been made the subject of much comment. In South China they constitute the commonest form of nervous disease. In India and West Africa meningo-myelitis is the commonest form of neuro-syphilis; tabes dorsalis and general paralysis being excessively rare.

Disseminated sclerosis is rare in most native races, and is not encountered in the Chinese.

Cerebrospinal meningitis occurs often in large epidemics, especially in the Southern Sudan, where sulphonamides have achieved remarkable results. It occurs in cyclical epidemics all round the fringes of the Sahara.

Acute meningococcal septicaemia, a fulminating disease with petechial hæmorrhages in the skin and conjunctiva, without neck rigidity and with clear or faintly opalescent cerebrospinal fluid, is not uncommon in Africans. Sometimes the meningococci may be demonstrated in blood-films. According to Bell (1944) this serious form also yields to sulphonamide therapy.

GOITRE

Simple parenchymatous or *colloid goitre* is extremely common in Egypt, in the Nile Valley, Sierra Leone, in the Caji districts of the French Congo, and in the Ouelle and Katanga districts of the Belgian Congo. It has been reported in Indonesia, especially in the Island of Bali. In India it is most common in the Himalayan and subhimalayan regions and in the parts drained by the great Indian rivers (McCarrison), as well as in the western provinces of China. Disorders of secretion resulting in exophthalmic goitre, myxœdema or cretinism are almost unknown.

It has been remarked that goitre is not found among the Bedouin or other desert tribes. In endemic goitrous districts iodine should be given to all girls between the ages of eleven and sixteen and to all pregnant women.

DISEASES OF THE EARS

Chronic otitis media with central tympanic perforation (mesotympanic otitis) is less common in the tropics: cholesteatoma (epitympanic otitis) is very rare.

Instillation of urine into the meatus is practised by witch doctors in New Guinea as well as the insertion of insects. In addition to these malpractices must be numbered the deformation of the pinna, perforations of the lobule, keloids and tribal marks.

MALIGNANT GROWTHS

There is no truth in the oft-quoted popular statement that malignant growths are unknown, or are very infrequent, among primitive peoples. The truth probably is that, age for age, they are as frequent as in civilized communities. The absence of accurate vital statistics, age records, or even registrations of births and deaths, make such a comparison difficult. There are, however, certain special features of malignant disease amongst natives.

The outstanding facts about malignant growths in the tropics may be stated categorically as follows:

- (1) The prevalence of primary liver carcinoma (12 per cent. of all carcinomata according to Vint), in 90 per cent. of cases grafted upon cirrhosis (Snijders). (Cazanove in French West Africa, Snijders and Straub in Sumatra, Strachan in South Africa, Smith and Elmes in East Africa, French observers in Dakar, Senegal.) In China (Snapper) primary carcinoma nearly always arises in a cirrhotic liver. Malignant changes in the bile ducts are far less frequent, but may be associated with *Clonorchis sinensis* infections (see p. 783). Berman (1956), in the Bantu in the Witwatersrand, found in young men that liver carcinoma accounted for 90 per cent. of all malignant growths; in Nigeria it is responsible for 70 per cent.; in Indonesia the figure is 79 per cent. and 31·5 per cent. in the Chinese population. It is predominantly a disease of young males with low nutritional standards, especially in those who have suffered from kwashiorkor in childhood (Kennaway).
- (2) The infrequency of gastric carcinoma.
On the whole gastric carcinoma is more common in people of African race in the Caribbean than in Africa itself and this is the case also in U.S.A. In Malaya the percentage is 1·3 per cent to all cancers, whereas in the Chinese it is 12·2 per cent. Kouwenaar (1955) ascribes this fact to the shorter life-span amongst native peoples. The percentage in males varies from 8·9 per cent in S. Africa to 17·5 per cent in Rhodesia, as against 29·8 per cent in Johannesburg.
- (3) The prevalence of malignant tumours on the sides of the neck.
- (4) The prevalence of skin carcinoma on legs and feet (grafted on chronic ulceration).

Many observers in recent years, especially Snijders, Straub and de Langen in the Dutch East Indies, Vint in East Africa and Rogers in India, have drawn attention to the fact that cancer should not be regarded as necessarily a scourge of civilization. Nor is it correct to state that the number of sufferers is increasing at a staggering rate. It was Hoffman, in compiling statistics for the United States Prudential Societies, who stated that the cancer rate was eight times as high amongst the 500 million of civilized races as among the 1,200 million uncivilized, including India; but Rogers's statistics, based upon 1,600 post-mortems in Calcutta, critically arrayed, showed no greater incidence of cancer in England than in India. The carcinomata were equally divided between the squamous

and glandular epithelial forms, but the frequency of epitheliomata of the jaws in Calcutta is notable, and has also been recorded by French observers in Dakar, Senegal.

Malignant tumours, including both connective tissue and epithelial types, are about equally common in Bengal and in England, with a slight excess in the tropical country; but both innocent and malignant connective-tissue tumours are considerably more common in Bengal than in England. Vint has shown that, as far as Central Africa is concerned, there is close agreement between figures for malignant disease in natives, both in Nigeria and in Kenya. The large number of squamous-celled cancers in the latter country is due to malignant changes in chronic tropical ulcers of the legs, and to epitheliomata associated with this condition.

Carcinomata of the œsophagus and nasopharynx are especially common among the Chinese. Burrell (1957) has recognized œsophageal cancer in the Bantu. Its incidence per 100,000 of E. London was found as high as 72·3. It is distinctly related to drinking illicit liquor. The common initial symptoms are retrosternal pain, and unproductive cough. Other symptoms are difficulty in swallowing, periodical vomiting and scalorrhœa with regurgitation.

A further peculiarity is the relatively high proportion of sarcomatous to carcinomatous growths. In the extensive series of 5,000 autopsies from the Indonesia, malignant growths were found in 9 per cent., and the proportion of sarcomatous to cancerous tumours was 1 : 3·9, whereas in Europe and America it is 1 : 10. Sarcomata of the very malignant round-celled type greatly predominate.

Malignant disease of the breast is not uncommon in the East African native and, according to Vint, in almost 20 per cent. of cases it is found in males. Sequeira and Vint have pointed out that malignant melanoma, next to squamous-celled cancer, is the commonest form of malignant disease in the natives of East and Central Africa, and O'Connor has stated that in Bengal malignant melanoma is distinctly commoner than in Europe. Most of the tumours are found on the foot, and the majority are on the plantar surface. Trauma is the most probable cause, as both sexes walk barefoot, and in a few instances "crab yaws" is an antecedent. The disease is usually locally malignant.

The clinical course of malignant growths differs, as a rule, between natives and Europeans. Through ignorance or fatalism, native patients resist to the very end before asking for medical aid, and are in a hopeless condition when discovered. Kaposi's sarcoma is not uncommon also in West and East Africa, but it is rare in Europeans. It is almost invariably diagnosed as angioma or fibroma with œdema and ulceration.

There still remain certain other peculiarities, consequent on local habits and customs. Thus Spittel, Davidson and Turner have shown that cancer (epithelioma) of the cheek is the commonest malignant growth in Ceylon, and is as frequent in women as in men between the ages of thirty-five and fifty; here, no doubt, it is due to irritation caused by betel chewing. In Travancore, South India, it is also common, so that out of 1,700 cases collected by Bentall it formed 70 per cent. Carcinoma of the paranasal sinuses are less common in the Bantu in Johannesburg. All cases occur in snuff-takers where it consists of various herbal mixtures and contains anthracene, fivoranthene and various pyrenes which are found in chimney soot.

Kangri-burn cancer is mainly found in Kashmir and is encountered in the older men. In the Mission Hospital there no less than 84 per cent. of the operations performed are for this condition. Kangri is an earthenware bowl 5-6 in. in diameter, surrounded by basket-work and surmounted by a wicker handle. It is heated by wood charcoal, and is worn against the skin under a

loose garment. The growths are commonly found on the inner side of the thighs and anterior surface of the abdomen, above or below the umbilicus. The heat given out by the kangri is estimated at 150–200° F. The growths usually commence in the scars of previous burns. There are no metastases.

Burrows, Molesworth, and many other observers in Australia, have drawn attention to epitheliomata of the face, especially in Scottish and Irish immigrants, attributed to excessive irradiation by the ultra-violet rays of the sun. Actinic hyperkeratoses, which may proceed to epithelioma, are common in all fair-skinned Europeans long resident in the tropics.

CHAPTER III

THE TROPICAL ANÆMIAS

The following abbreviations are used in this subject:

- CI = Colour Index. $\frac{\text{Hæmoglobin (percentage of normal)}}{\text{Red cells (percentage of normal)}} = \frac{100}{100} = 1.$
MCV = Mean corpuscular volume.
MCH = Mean corpuscular hæmoglobin.
MCHC = Mean corpuscular hæmoglobin concentration.
E.S.R. = Erythrocytic sedimentation rate.

Anæmia at present constitutes a major tropical disease. According to Foy and Kondi (1957) the lowest mean hæmoglobin rates are found in the hot damp river valleys of the Brahmaputra and Surma (Assam) at 300–600 feet. Here the mean hæmoglobin for all groups is 10.9 gm./100 ml. with 16.5 per cent. of the population having levels below 8 gm./100 ml. The lowest levels are in pregnant women. The lactating ones were more than 1.0 gm. higher. Portuguese E. Africa is an area of similar climatic conditions, but hotter with a more extended dry season. There the mean hæmoglobin level of the rural population was 10 gm./100 ml. with 92 per cent. below 8 gm.

In high altitudes, as at Darjeeling (2,500–8,000 ft.) and the Nilghiri Hills (3,000–6,000 ft.), there is an increase of the mean hæmoglobin levels of the population with very few below the 8 gm. mark—this is probably attributable to altitude. In Ceylon the mean hæmoglobin was higher than in India or Africa. Amongst pregnant women the mean was 11.0 gm. with only 11 per cent. below 8 gm.

The evidence is that severe anæmia is widespread through India, Ceylon and Africa and that 85 per cent. have normal to low MCV, low MCH and MCHC, together with erythro-normoblastic marrow with giant stab cells, indicating that there is iron-deficiency and this responds well to 15–35 gr. of oral ferrous sulphate taken over a period of 2–4 months. The remaining 15 per cent. have normal high or low MCV's, MCH's and MCHC together with *megaloblastic* marrow responding to folic acid and vitamin B₁₂, and so it comes about that *iron*-deficient anæmias are far more common in hot, damp areas while the *megaloblastic* are prevalent in cooler atmospheres, although both types may be found in the same regions.

The serum B₁₂ levels in the iron-deficient are well within the normal range, but in megaloblastic cases they may be low. A low dietary intake of B₁₂ does not always lead to low serum levels or even anaemia, as it may become available from biosynthesis of the intestinal flora.

Iron-deficient Anæmias.—The ætiology is still uncertain as there is no evidence of widespread deficiency of dietary iron. It is probably due (1) to poor absorption of iron, (2) to excessive dermal losses of iron on account of climate, (3) pregnancy and lactation occurring below the age of 19, thus coinciding with rapid growth, (4) blood loss to intestinal parasitism, (5) quantitative and qualitative protein changes in the diet.

The iron needs for hæmoglobin synthesis are 27 mgm. daily, of which 20 mgm. are supplied by the normal distintegration of blood corpuscles, so that, with excessive losses and poor absorption, the iron balance is easily upset. In the tropics, in spite of high dietary iron, the incidence of iron-deficient anæmia is much greater than in Europe or U.S.A. The composition of the diet has an important effect on iron absorption. Excessive dietary phosphorus, high phytic acid and low calcium intake also interfere with its absorption. The high cereal diets of the Indian and African rich in these substances tend to produce this state, and it is possible that they encourage the production of bacteria which synthesize phytase.

Folic acid affects iron absorption, in the presence of low gastric acidity. Iron is normally lost in the faeces, bile, urine, hair, sweat and in the female by reproduction losses. The estimations of the amount of iron in sweat vary. When sweat is collected in a thermostatically controlled room and in a bath, as well as the "reflex" sweat in plastic bags, it has been shown that 0.3-6.0 mgm. per litre can be lost. Then in the tropics 2-11 litres of sweat may be secreted daily, and thus a negative iron balance ensues. The iron requirements of women during the reproductive period is 4-10 times greater than those of men, thus contributing to their higher incidence. Menstrual losses, pregnancy and lactation must also be taken into consideration.

In the past ancylostomes and malaria have been regarded as the chief factors, but now it is realized that most anæmias are nutritional in origin. Macrocytosis may be seen occasionally in iron-deficient anæmias. Iron-deficient anæmia is the same as chlorosis which formerly was widespread in England. It is now known as hypochromic, microcytic anæmia. It is generally more noticeable in young native girls in the first year after katamenia has set in. Some even have spoon-shaped nails (koilonychia) with stomatitis and dysphagia.

Nutritional Megaloblastic Anæmia.—Though frequently associated with malaria, syphilis and ancylostomiasis, this type of anæmia results from a deficiency of the "extrinsic factor" which in most cases is folic acid. This is in marked contradistinction to pernicious anæmia which is caused by malabsorption of vitamin B₁₂, due to lack of the "intrinsic factor." Usually a hæmolytic element is superimposed upon the primary deficiency.

The blood picture is characterized by macrocytosis, with a red-cell diameter of 8.4 μ and MCV ranging from 100-145 cu. μ , and by leucopenia. Usually the red cells are fully hæmoglobinized but sometimes an independent iron deficiency may reduce the MCHC to about 26 per cent., thus lowering the colour index to unity or below.

The sternal marrow is characterized by megaloblastic hyperplasia associated with many metamyelocytes. In the early stages large numbers of macronormoblasts with precocious hæmoglobinization, together with metamyelocytes, may be found. Sometimes there may be bilirubinæmia and urobilinogenuria as in pernicious anæmia, but HCl is present in the gastric juice, or can be evoked by histamine stimulation.

The majority react satisfactorily to folic acid, but some may also require vitamin B₁₂, liver extract by injection, or proteolysed liver by mouth. It

has been shown in Kenya by Foy and Kondi that oral and parenteral penicillin have a remarkable effect on this anæmia by eliminating from the intestinal flora a variety of organisms which compete with the body successfully for the available supplies of vitamin B₁₂. The dosage is 200,000 units orally, or 400,000 units parenterally daily for 10–12 days.

Megaloblastic Anæmia of Pregnancy.—In India in peasant women this is known as Wills' anæmia, but is common in people of that race the world over—in Fiji (C. Manson-Bahr), in Malaya, W. and E. Africa, and in Macedonia (Fairley). HCl and pepsin are present in the gastric juice, while bilirubinæmia and urobilinogenuria may be found. Owing to demands of the foetus iron-deficiency may be superadded. This anæmia usually comes on in the second month, but final breakdown may be sudden. The tongue may be sore. Oedema of the feet and ankles are usually associated with low blood pressure and pyrexia. Retinal hæmorrhages are common. The anæmia is apt to recur in subsequent pregnancies. Response to folic acid and liver therapy is very satisfactory.

Baghdad spring anæmia.—A form of acute anæmia has been reported in Baghdad, appearing only for a few weeks in spring. This anæmia, according to Lederer, runs a very rapid course, and a severe degree is produced within 24 to 36 hours. The mortality is about 10 per cent. It is curable by blood transfusion, liver therapy in massive doses and injection of adrenalin. The disease is confined to boys, for the main part Jews, especially those of a certain constitutional type. It is suggested that the hæmolysis is due to anaphylaxis by contact with flowers (*Verbena hybrida*) and young fruits. The administration of blood has a double effect, counteracting shock as well as stimulating the bone marrow. In mild cases whole blood injections (10–20 ml. intramuscularly) suffice; but in severe degrees intravenous transfusions are necessary.

Favism.—This is an acute hæmolytic anæmia due to allergy, to eating the vetch—*Vicia faba*—or to its pollen, when inhaled. It has a curious distribution, being relatively common in Sardinia, Sicily, Calabria (S. Italy) and the Balkans, while Baghdad's Jews, who were deported to Israel in 1952, showed a particularly high incidence. A familial susceptibility to the disease exists and it is found more commonly in boys than in girls. Recent researches in Israel (Szeinberg and others, 1957) have demonstrated a significantly lower glutathione content of the erythrocytes in those who have shown evidence of the disease, than in other members of their families. This genetic enzyme deficiency appears to be due to familial susceptibility, while sex-linkage may explain the greater frequency in males.

The disease, while common in Asiatic Jews, especially those from Baghdad, is rare in European Jews. This recalls that the Jewish community of Baghdad are pure descendants of the captives carried away to Babylon by Nebuchadnezzar and also that the Romans despatched a Judæan garrison to Sardinia in the second century B.C. Available evidence suggests that the basic genetic biochemical anomaly which arose in Judah in early times has been carried by emigrant Jews to Baghdad and over the

Mediterranean littoral. The symptomatology is identical with Baghdad spring anæmia described above.

Lymphatic leukæmia and spleno-medullary leucocythæmia appear to be met as frequently as in Europe.

Thrombocytopenia vera is not uncommon in S. China and is undoubtedly to be found in many native races (*see* Onyalai, p. 685).

SICKLE CELL DISEASE AND THE HÆMOGLOBINOPATHIES

The Hæmoglobinopathies.—Hæmoglobin comprises an iron-containing porphyrin complex or *hæm*, combined with globin, which is comprised of a chain of polypeptides derived from many different amino-acids. The

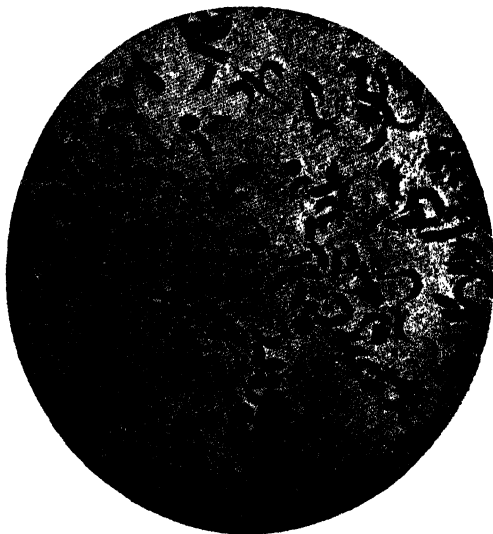


Fig. 1.—Sickle cells. Fresh blood preparation after forty-eight hours. (*Bulletin of the Johns Hopkins Hospital.*)

composition and positioning of the polypeptide residues in the chain is under genetic control, and, as has been shown by Ingram (1956), that in the case of the S, or sickle variant, the substitution of a single polypeptide may alter significantly the physical properties of the hæmoglobin molecule. Mutations giving rise to these subtle biochemical variations have led to the distribution in the human race of a range of abnormal hæmoglobins, in addition to adult or "A" and foetal or "F," designated "S," "C," "D," "E," "G," "H," "I," "J," "K" and "L." Their production is governed by a series of allelomorphic *genes* which behave as Mendelian dominants; the inheritance of which may be heterozygous (the abnormal genes one from one parent only), or homozygous (due to abnormal genes,

one from each parent). A simple diagram (Fig. 2), designed to show the proportionate distribution of the genes governing the formation of A, or adult, or S or sickle hæmoglobin in the children resulting from the marriage of two "sickle" heterozygotes serves to explain the principles involved. Hæmoglobin S, or sickle hæmoglobin, differs from normal adult, or A hæmoglobin, in that a polypeptide residue derived from the amino-acid-valine is substituted for one derived from glutamic acid in the A hæmoglobin polypeptide sequence (Ingram, 1956). Hæmoglobin S differs from A in two respects; it is far less soluble in its reduced state, and its mobility towards the anode, an electrophoresis at pH 8.6, is less than that of A. Under conditions of reduced oxygen tension the molecules of hæmoglobins

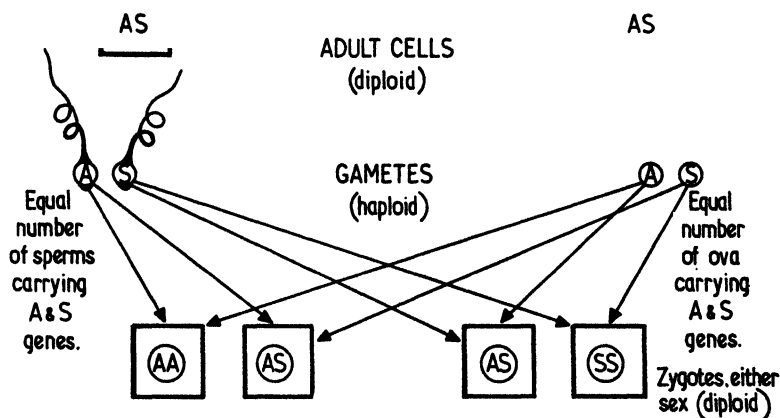


Fig. 2.—Diagram of Transmission of Genes.

align themselves longitudinally to form filamentous liquid crystals called tactoids which characteristically distort the red cell envelope.

The erythrocytes of the AS heterozygote contain both A and S hæmoglobin, the former predominating; owing to the low concentration of S hæmoglobin tactoid formation does not occur until a partial pressure of oxygen, as low as 20 mm. Hg, is reached. Since so low a tension is not found under normal physiological conditions, intravascular sickling only occurs very exceptionally and the condition referred to as "hæmoglobin S trait," is without clinical manifestations, except under conditions of grave anoxia, as in high altitude flying without oxygen supplies. The homozygous condition in which the erythrocytes contain only S hæmoglobin and a small, variable supplement of F, or foetal hæmoglobin, results in a grave type of chronic hæmolytic anæmia designated "sickle-cell anæmia." In most instances, sickling begins to occur at partial pressure of oxygen between 60 and 40 mm. Hg, while the percentage of sickled erythrocytes approaches 100 per cent. at 20 mm. Hg. Since the oxygen tensions are

within the physiological range in the capillaries of many organs, intravascular sickling can readily occur provided, as shown by Allison (1956), that the time of exposure to these low tensions exceeds 2 minutes, compared with the normal time of passage through the capillary bed of 15 seconds. Prolonged segregation of sickled cells in the spleen, possibly through loss of potassium, perpetuates the deformity in a proportion of them. Since sickled erythrocytes have an increased mechanical fragility, this moiety of irreversibly sickled is rapidly lysed, and a state of chronic hæmolytic anæmia results. The presence of sickled cells which obstruct the smooth flow of blood cells through the capillaries, leads to increased viscosity, so that a vicious circle of stasis, increasing deoxygenation and consequent increased sickling may be established in many organs and may result in multiple capillary infarction. This constitutes the most dangerous aspect of this disease. Increased coagulability of the blood, possibly due to excessive liberation of thrombokinasé, has also been reported. The lives of patients suffering from sickle-cell anæmia are dominated by recurrent "crises," the majority of which, as pointed out by Diggs (1956), are manifestations of capillary infarction, while exacerbation of hæmolysis and phases of marrow depression from intercurrent infections, may cause dangerous reduction in the red cell concentration. The majority of sickle-cell hæmozygotes die in crisis before puberty, but in those who do survive to adolescence the crises become infrequent and less severe. Pregnancy, carrying with it an enhanced risk of crises, is rarely survived, however, though a few males and unmarried women may attain middle life.

Geographical Distribution.—The gene of S hæmoglobin is widely distributed throughout the Negro races, though it is very rare south of the Zambesi. It has been carried to the Caribbean Islands and to North, Central and South America. An independent focus has been found in the Thrace area of Greece by Caminopetros, and may have spread thence to the whole Mediterranean littoral. It is found at a low incidence throughout Arabia; it also appears in the primitive Veddoïds of Western India, and amongst races who have intermarried with them. An interesting suggestion has been made by Lehmann (1956-57) in explanation of the wide distribution of the S gene. In neolithic times, the Arabian peninsula, which was then well-watered and fertile, was inhabited by an early Veddoïd race, in whom the gene arose by mutation. One section of this race later migrated down the western side of the Indian Peninsula, another crossed into East Africa and a third may also have spread north into Asia Minor, each carrying the S gene with it. This S gene is not found in the Negro races of the Indian and Pacific Oceans, nor in Australian aboriginals. The incidence of the sickle-cell trait shows great variation between localities, rates as high as 40 per cent. being reported from East Africa, 20-25 per cent. from W. Africa, and 9 per cent. in U.S. Negroes. The cause of this variation, and also the persistence of high gene frequencies, despite the loss of many S genes through the premature death of S homozygotes, is not completely understood. The production of new S genes by mutation has not been observed. It seems probable that some mechanism, or mechanisms, tend to preserve selectively the heterozygous carriers of the S gene, a process termed "balanced polymorphism." Allison (1954) has brought

forward evidence that *P. falciparum* malaria fulfils this rôle, pointing out that high S gene frequencies occur in highly malarious areas, whereas in a non-malarious area, where children who do not carry the gene have as good a chance of survival as those that do, the incidence is lower. This equality of survival, together with the elimination of many S genes through the early death of the sickle-cell homozygotes, would tend to dilute the S genes in the population within a few generations. This may explain the low incidence of the sickle-cell trait among the Negroes of the United States (9 per cent.), relative to that of the 20–25 per cent. among West African races, from whom they have descended. Allison's theory has not gained universal acceptance, and the matter remains open.

Methods of demonstrating sickling.—

1. The sealed drop method.

A drop of blood is obtained by finger-prick and is placed on a glass slide. A cover-slip is applied and mingled with warm paraffin wax or vaseline. After incubation at 37° C. for 24 hours, the oxygen uptake of the leucocytes will be found to have caused sickling among the erythrocytes.

2. The bacterial reduction method.

A drop of blood is sealed beneath a cover-slip after it has been mixed with a small drop of a suspension of *Bacterium coli*. After 24 hours' incubation, sickling of the red cells is evident.

3. The chemical reduction method.

A drop of blood is mixed with a drop of a freshly-prepared 2 per cent. solution of sodium metasulphite. A cover-slip is superimposed, but ringing is unnecessary. Thirty minutes' incubation at 37° C. suffices to produce sickling.

Sickling tends to be of two types. That seen in the heterozygous condition (sickle-cell trait), is described as resembling a holly leaf, and must be distinguished from crenation in stale or drying red blood cells, whereas in the homozygous condition (sickle-cell anæmia), the deformity is of the much more arresting filamentous form.

Pathology of Sickle-cell Anæmia.—The pathological lesions comprise those of a chronic hæmolytic anæmia together with the effects of multiple capillary occlusion. The red marrow is abnormally extensive; the diploëic space of the skull is widened and the outer table may be eroded over the vertex. There is marked normoblastic hyperplasia and some increase in the primitive cells hyperplasia and some increase in the primitive cells of the granulocyte series. In wet, unstained marrow preparations, a mycelium-like fibrinoid network may be seen (Vanderpitte and Louis, 1953). Ectopic foci of hæmopoiesis may be found, especially in the liver. The spleen in early years shows grossly dilated sinusoids packed with sickled erythrocytes, while both erythropoiesis and phagocytosis of sickled cells is evident. Later, as a result of repeated infarction, it is reduced to a fibrotic vestige, containing calcium and hæmosiderin crystals deposited without formation. The liver, which undergoes progressive enlargement with increasing age, shows, *pari passu*, increasing fibrosis. In early life

the sinusoids, which are dilated, contain hypertrophied Kupfer cells, leucocytes in profusion with here and there plugs of interlocking sickled erythrocytes. A fine fibrinoid reticulum of uncertain origin usually spans the lumen. As the years pass, the stroma becomes thickened and distorted by plaques of dense fibrosis at the sites of multiple small infarctions. If adult life is attained, the liver usually shows a characteristic type of fibrosis on which nodular regeneration may be imposed. Multiple infarctions may also be found in the kidneys, brain or bones.

The bones themselves may display characteristic lesions from an early age. Ischæmic necrosis of the shaft with marked periosteal new bone formation is also seen. Subsequently, while growth may be arrested by interference with the vascular supply in the proximal epiphyses, infarction of the diaphyses of any major long bone, such as the femur, humerus or tibia, may be found, while ischæmic necrosis of the femoral head, simulating Perthes' disease, is a well-recognized complication. Hæmatogenous bacterial infection may be implanted on the infarcted area, the condition then closely resembling primary osteomyelitis. The radiological and pathological changes in the skull are indistinguishable from those of thalassæmia major, though they are to be found only in a minority (10-20 per cent.) of patients (Fig. 3).

Symptomatology.—Owing to the inhibitory action of fœtal hæmoglobin on sickling, symptoms of the disease are not manifested in the early months of life during which a considerable proportion of hæmoglobin F persists, but with its decline and the associated increase in the hæmoglobin S concentration, which takes place from the fourth month onwards, the disease begins to declare itself. Impaired growth, anæmia with splenomegaly and slight icterus, and recurrent crises mark the progress of the disease. Stunting is commonly associated with a characteristic facial and bodily conformity, the skull being enlarged, sometimes with remarkable frontal and bi-parietal bossing, while an accentuated medial epicanthic fold and prominent malar bones confer a Mongoloid appearance: the trunk is disproportionately short while the limbs are long and slender. Puberty is often delayed and sexually immature adults may be encountered. The spleen, which is invariably enlarged at some period during the first five years, as a result of multiple infarction, tends to shrink beneath the left costal margin as age increases. Hepatomegaly which commonly appears before the age of ten years, becomes the rule in the second decade; in surviving adults the liver may be found much enlarged, hard and irregularly nodular. The anæmia is typical of chronic hæmolysis, but is subject to fluctuations due to crises of two types, that due to an exacerbation of the hæmolytic process and that resulting from transient inhibition of erythropoiesis. The former may be precipitated by intercurrent infections and, in some instances, by pregnancy. The latter is commonly due to systemic infections. The anæmia with red cell counts, ranging between 2 and 3·5 million, is macrocytic, but the cells are fully hæmoglobinized. There is a high, but variable, reticulocytosis and, usually, a considerable leucocytosis in which either polymorphs or lymphocytes may predominate. The stained film of fresh peripheral blood shows macrocytic anisocytosis, nucleated erythroblasts, whose numbers may equal, or even exceed, that

of the leucocytes, and a few sickled erythrocytes. (The last are never found in the fresh blood of sickle-cell heterozygotes.) The platelet count tends to be increased. The serum is usually faintly icteric, and, though in early life this is due to an excess of pre-hepatic bilirubin, owing to increasing liver damage with increasing age, by the second decade a rising level of direct-acting ("post-hepatic") bilirubin is often found. An excess of fibrinogen has been noted (Fenichel, Watson and Eirich (1950), also increased prothrombin activity (Walters) while coagulation time may be shortened. The marrow shows great normoblastic hyperplasia with some increase also in the myeloid series and in the megakariocytes. In Nigeria



Fig. 3.—X-ray of skull in sickle-cell disease, showing widening of cortex and "hair on end" appearance. (*Dr. J. H. Walters.*)

Berry (1956) has noted evidence of the deficiency in the hæmopoietic factor, namely macro-normoblastosis with precocious hæmoglobinization, giant metamyelocytes and even megaloblastosis. Crises, which are usually marked by pain and fever, exhibit a variety of patterns. As pointed out by Diggs (1956) the great majority are manifestations of acute vascular occlusions, a small proportion only reflecting phases of increased hæmolysis or of marrow aplasia. Joint pains, often associated with synovial effusion, occur very commonly while, as noted in E. Africa by Trowell, Raper and Welbourn (1957), painful swelling of the metacarpals, metatarsals and phalanges is very frequent. Of equal importance is the abdominal crisis,

comprising fever and tympanites, due to a degree of ileus. These attacks, provided they do not provoke surgical interference, which is harmful, usually subside on conservative treatment within 48 hours. The probable mechanism is widespread mesenteric capillary occlusion. Fatal shock may, however, terminate such an attack and in these instances acute thrombosis of the splenic vein or multiple small infarctions in liver, kidneys and suprarenals are to be found. Fever with renal pain and hæmaturia provides another common event. Vascular occlusion may cause focal damage to any part of the central nervous system of which hemiplegia is a common well-recognized manifestation. Retinal scars may be observed while Tarbies has described miliary aneurysms of the retinal vessels. Painful, though transient, subcutaneous nodes may develop at any site. The heart is usually overactive and dilated; it may show signs of either right or left ventricular failure. In addition to functional hæmic bruits relative incompetence of the mitral or tricuspid valve often gives rise to characteristic murmurs. A slight or moderate degree of finger clubbing is often to be seen. Chronic ulceration of the legs is very common in adults. They are also seen in cryptogenic splenomegaly in Hong Kong, especially in males. Pigmentation is due to deposits of iron within macrophages in the dermis (McFadzean and Tsang, 1958).

Treatment.—This is unsatisfactory at the present time. Iron and liver extract, except in those cases who show evidence in the marrow of lack of essential hæmopoietic substance, are of little benefit, though repeated blood transfusions may be of transient benefit during the rare hæmolytic or aplastic crises. Splenectomy is not indicated, save in young children with very acute hæmolysis and greatly enlarged spleens. As a vascular relaxant *Priscoline* has been advocated by Seavell (1954) for relief of pain in crises, but anticoagulants, such as *Tromexan* and *Dindivan*, suggested by Griffiths (1955), are of little avail. Recently the employment of acetazolamide (*Diamox*) has been suggested by Hilkovitz (1957) on the grounds that this inhibition of the enzyme carbame anhydrase tends to block the release of oxygen from the hæmoglobin, though not to such an extent as to cause serious tissue anoxia. He has demonstrated a significant reduction in the proportion of permanently sickled erythrocytes in fresh blood following a dosage of 7 mgm. per kilo body weight of this drug, but the results of an adequate clinical trial are still awaited.

Other hæmoglobinopathies of clinical importance.—Hæmoglobin C appears to have originated in the Northern regions of Ghana, where Edington and Lehmann (1956) have found an incidence of the trait exceeding 15 per cent., which was higher than that of the hæmoglobin S trait. The gene appears to have spread laterally from this focus to a limited extent only, as far as the delta of the Niger, and has been carried to the New World, where it was first discovered in a North American Negro family. Where both C and S genes coexist, there is some tendency for the former to replace the latter since, according to Allison (1956), the hæmoglobin C trait affords a selective protection comparable to that of the S trait, while there is no loss of genes due to premature death of the homozy-

gotes as in sickle-cell anæmia. The clinical importance of this variant is its frequent association with hæmoglobin S for the heterozygous S.C. endowment gives rise to chronic hæmolytic anæmia with splenomegaly, which, though of variable severity and always less grave than that of sickle-cell anæmia, may nevertheless cause considerable disability in the rare instance in which anæmia appeared relatively benign and thrombotic phenomena were lacking. As in all the non-sickling hæmoglobinopathies, the presence of hæmoglobin C is associated with numerous target-shaped erythrocytes in the peripheral blood. Hæmoglobin D is found in the North Western regions of the Indian Peninsula, in Sikhs, and Punjabi Hindus, but gives rise to no symptoms. Hæmoglobin E, however, is of importance in Burma, Thailand and the Malay Peninsula, where incidences exceeding 10 per cent. have been found, while a few examples have been imported from Indonesia, Sarawak and Ceylon, in which island the gene is confined to the Veddah races. In the very occasional examples of homozygous hæmoglobin E disease which have been recognized, a mild macrocytic anæmia, with numerous target cells, but without increased hæmolysis, has been associated with slight hepatosplenomegaly.

Hæmoglobin H has so far been demonstrated in a Chinese family in the United States (Rigas, 1956), in a Gurkha woman (Brain and Vella, 1958) and in Liberia (Neel) and also in Greeks. The homozygous disease has not been found, but in the individual, in whom the genes of hæmoglobin H and thalassæmia are combined, a refractory microcytic, hypochromic anæmia with reticulocytosis, increased osmotic resistance and shortened cell survival time is found. Under conditions of anoxia, especially at an acid pH, hæmoglobin H forms an intra-erythrocytic precipitate which can be demonstrated by supravital staining with brilliant cresyl blue. A moderate degree of splenomegaly occurs.

Thalassæmia, Cooley's or Mediterranean anæmia is a genetic disease in which the development of a normal adult "A" hæmoglobin is suppressed; as a consequence foetal or "F" hæmoglobin persists throughout life. The gene determining this anomaly is not an allelomorph of the genes governing hæmoglobins A to L, though its association with any of them may give rise to an anæmia of symptomatic degree. The homozygous inheritance of the thalassæmia gene gives rise to a grave hæmolytic anæmia—*Thalassæmia major*—which usually proves lethal in the first decade, but the heterozygous condition, called *Thalassæmia minor*, may vary in intensity from the asymptomatic *Thalassæmia minima* to a severity approaching that of the first-named.

The gene is now known to have a very wide distribution. Originally recognized in peoples of Mediterranean stocks, it is frequent in Burma, Thailand and Indonesia and has been recognized, though rarely, in West Africa, Arabia, Persia and India. Israëls and his associates has even discovered it in those generations of a Scottish family, in whom the possibility of an admixture of Mediterranean blood was remote (Israëls, Suderman and Hoogshaten, 1955). A detailed description of the disease is beyond the scope of this book; it must suffice to describe in itself the dominating features of *Thalassæmia major*. The characteristic is the "leptocyte," a wide, thin cell showing the "target" or "Mexican hat"

anomaly (*see* p. 1097) in which the concentration of hæmoglobin is low, yet ample stocks of free iron can be demonstrated in the marrow and the serum iron concentration, in contrast to that seen in hypochromic anæmia due to iron deficiency, is normal or high. There is a marked resistance to lysis in hypotonic saline, yet the cell-survival time is much reduced. A high sustained reticulocytosis is associated with the presence of numerous erythroblasts in the peripheral blood; a leucocytosis is common in which lymphocytes may predominate. The clinical picture comprises stunting, infantilism, marked enlargement of the spleen and liver, bossing of the skull and a mongoloid facies. There is radiological evidence of osteoporosis due to marrow hyperplasia, while the skull may show widening of the diploëtic space, erosion of the outer table and the vault, the formation of new bone in vertical spicules producing a dramatic "hair-on-end" appearance. The importance of this gene in tropical practice lies in the fact that its association with the genes of S, C, E and H hæmoglobins results in a significant degree of anæmia. In fact, the association in the case of hæmoglobins E and H appears to be essential in order that they may assert themselves. In the double heterozygote of S and thalassæmia, a severe, though non-lethal type of hæmolytic anæmia termed *micro-drepanocytic disease* occurs, while a very similar condition is found as Hæmoglobin-C-Thalassæmia Disease.

Recognition of the hæmoglobin variants.—Details of the physico-chemical methods used must be obtained from original publications; they are beyond the scope of this book. Electrophoresis by the paper strip method, or by a starch medium of stroma-free solution of the hæmoglobin under examination, and against known controls, is the one most often employed. A barbiturate buffer solution at pH 8·6 is the electrolyte most often in general use. The relative speeds at which the hæmoglobin variants move towards the anode at this pH has been expressed diagrammatically (Lehmann, 1957). It will be noted that hæmoglobins D and S have a similar mobility, but can be distinguished by sickling and solubility tests, since the former remains highly soluble, even when deprived of oxygen, does not form tactoids and therefore does not cause the sickle deformity. Hæmoglobin H can be distinguished from I by electrophoresis at pH 6·5, since it alone remains in union at this reaction and is therefore unique in moving towards the positive pole. Fœtal hæmoglobin likewise cannot be separated from adult A hæmoglobin by electrophoresis, and is usually estimated by means of its resistance to dematuration by alkalis which destroy hæmoglobin A. The "one minute" dematuration of Singer, Chernoff and Singer (1951), is in general use. In some instances, recognition of the type of hæmoglobin present in the blood of a proportion provides insufficient evidence on which to determine their hæmoglobin genotype. For instance, a patient, whose corpuscles contain only hæmoglobins S and F, may be a sickle-cell homozygote, or he may be a double heterozygote for the genes of A and S and also thalassæmia, when the latter has suppressed the formation of the hæmoglobin A moiety which should be present in the blood of an AS heterozygote. In such cases investigation must be extended to the parents, when, in the instances quoted above, either both

parents would prove to be carriers of the sickle-cell trait, or one a carrier of this trait and an example of *Thalassæmia minor*. This field of research is expanding with great rapidity and standard text-books can aspire only to set out the principles involved and the facts which are of significant clinical importance.

Many other hæmoglobins have recently been recognized, but their significance has not in all cases been determined.

Section I.—FEVERS

Subsection A.—FEVERS CAUSED BY BLOOD PROTOZOA

CHAPTER IV

MALARIA

Definition.—The term malaria includes all fevers produced by endoparasitic parasites of the genus *Plasmodium* which give rise to periodic fevers.

Geographical distribution.—*Benign tertian malaria* in Europe extends to 65° N. (Lake Ladoga, Archangel and S. Sweden). It is still to be found in Denmark, Holland and Emden district of Germany; was until recently endemic in S.E. England. In May and June, 1953, Crockett and Simpson discovered two cases of indigenous *vivax* malaria living in adjacent houses in Stockwell, London. The vector is probably *Anopheles plumbeus* which breeds in tree holes. The carrier in N. Europe is *Anopheles atroparvus*. In America it extends to 40° N. in Sacramento Valley and in Canada to 44° N. on L. Ontario. In the southern hemisphere it extends to 20° S. in Queensland, 30° S. in Natal, and 40° S. in S. Argentine. Malaria is rare above 6,000 ft. but is found in Quito (8,500 ft.), Addis Ababa (8,400 ft.) and in Londiani, Kenya (7,800 ft.). It is uncommon in W. and E. Africa. This parasite was introduced, probably from Madagascar and the latter, in the middle of last century to Mauritius and Réunion.

Barbados is free from malaria (though a small epidemic broke out in 1927) and so are the islands of the Pacific, E. of 170° E.

Ovale tertian malaria, identified in 1922, is a particularly mild form of fever with tertian periodicity and occurs for the most part in Central Africa, and is found in Sierra Leone, the Gold Coast, Nigeria and Uganda. A few infections have been reported from Turkmenistan, Palestine, Egypt, Mauritius, Venezuela, India, the Philippines and New Guinea.

Quartan malaria until comparatively recently appears to have been commoner in temperate latitudes than in the tropics. It is recorded from Central Europe, sparingly in the Mediterranean area—in Italy, Macedonia, Palestine—Iraq, South India and the Andaman Islands, and is the dominant form in South Ceylon (except in epidemic outbreaks), in parts of Malaya and in the Maldivé Islands. In Africa it is found sparingly, especially in the central portion. In West Africa, especially in children, *P. malariae* may be associated with *P. falciparum* in half the cases who show the former infection, while purely quartan infections are not rare. In America it is uncommon in the West Indies, but common in Antigua, Panama and Brazil. In Macedonia and the Caspian area the maximum incidence is from July to November, and in many localities it appears to be confined solely to children (from 2–10 years) as, for instance, in Salonika and the Western Solomon Islands.

Subtertian malaria is much more “tropical” in its distribution. It is

limited by the mean summer temperature of 70° F. (21° C.) and a mean winter isotherm of 48° F. (5° C.). In Europe it is rare, except in the Balkans and the Danubian marshes, but in the tropics it is the prevalent form, wherever fever is specially virulent. In 1920 subtertian malaria was imported into Central Russia by refugees from Turkmenistan and spread as far north as Moscow where cases occurred even during the winter season. It is found in desert oases, especially in Somaliland where it occurs in great epidemics after the rains. The vector, *A. gambiae*, disappears in the dry season when larvæ are found in the deep wells (M. T. Gillies). Subtertian is the chief form found in almost the whole of West and Central Africa, Asia Minor and in parts of Malaya and Central India. In the American continent it was formerly abundant in Panama and constituted a menace in North and Central Brazil. Although this form is usually not met at high altitudes, Garnham has recorded severe epidemics at Londiani, Kenya, at 7,800 ft. on farms where African squatters live. From February to May the mean temperature is 61° F. and *A. gambiae* the vector—a species which in that area spends most of its life in human habitations where the temperature is 5–10° F. higher than outside. In that situation the mean temperature is 66° F., which suffices for the sporogony of *P. falciparum*. Heisch and Harper have described an epidemic of malaria in Kericho, in the Kenya highlands, where the vector is *A. funestus*.

Epidemiology and endemiology.—Conditions which favour the presence and breeding of anopheles mosquitoes tend to the increase of malaria, and *vice versa*, and, whatever favours access of these insects and the parasites they contain, also favours the acquisition of malaria.

In subtropical regions subtertian malaria is a primary infection in summer and early autumn, hence the popular term—*æstivo-autumnal fever*. This peculiarity can be explained to some extent by the higher atmospheric temperature required for its development in the mosquito. Hence, though benign and subtertian forms are frequently associated, and the latter can be acquired at any time in the tropics, it is only in the summer and early autumn that subtertian can be acquired in more temperate zones. When the temperature falls below 15° C. development of the oöcyst in the mosquito is arrested, but when once the sporozoites have entered the salivary glands, they are capable of infecting man, even during the winter season.

Wenyon explained the seasonal variations of the two dominant forms of malaria in Macedonia and Palestine by the fact that the benign tertian tends to relapse over a longer period and is more resistant to quinine and chloroquine, whilst the subtertian is more amenable to treatment and there is less tendency for infections to persist from one season to the next.

Immunity produced by previous infection is another consideration (see p. 68). D. B. Wilson states that subtertian malaria causes little illness in the adult Bantus of parts of Tanganyika, though all babies are infected in their first few months of life, and suffer severely before immunity is acquired. The same holds good throughout West Africa.

As a rule, malarial infection declares itself a week or ten days after the infective bite of a mosquito. In some *vivax* strains of the temperate zone

the incubation period may be greatly prolonged; the benign tertian malaria in Holland, for instance, is due to infection acquired during the preceding autumn. This is known as "long latency." Full infection takes place in July and August, reaching its peak in the autumn months. Swellengrebel believes that from June to August, *A. maculipennis atroparvus* mosquitoes fly in and out of houses to lay eggs and so any infections acquired are injected into domestic animals, but in September, being a semi-hibernating mosquito, egg-laying ceases, but *atroparvus* continues to feed on blood and they remain in the houses. Therefore the infections they then acquire are passed to *man only*. On the other hand, the Madagascar strain of *P. vivax* differs in the length of the latent period which is, on an average, 12 days. Long latency is exceptional. There are also differences in the number of merozoites. In this respect it is identical with tropical strains such as the Chesson strain of Coatney. At least 3 types of *vivax* strain may be discerned.

- (1) St. Elizabeth type of temperate zone.
- (2) Netherlands strain of temperate zone.
- (3) Strains of the tropical zone, including Madagascar and Chesson.

Moreover, it has been established that these strains differ in their ability to develop in *Anopheles m. atroparvus* and in the number of oöcysts produced (Shute).

Malaria incidence is usually *endemic*, but *hyperendemicity* is a distinct form, demanding for its production such an intensity of transmission that a high degree of tolerance to the effects of reinfection is induced in those who experience its effects over a number of years, especially as a result of repeated infections in early childhood.

The World Health Organization has proposed the following classification:—

- I *Hypoendemic Malaria* with spleen rate in children 2–10 years of age 0–10 per cent.
- II *Mesoendemic Malaria* with spleen rate in children 2–10 years of age 11–50 per cent.
- III *Hyperendemic Malaria* with spleen rate in children 2–10 years of age constantly over 75 per cent. Spleen rate in adults is also high.
- IV *Holoendemic Malaria* with spleen rate in children 2–10 years of age constantly over 75 per cent. Spleen rate in adults low; it is in this type of endemicity that the strongest adult tolerance is found.

Macdonald (1953), by applying higher mathematical calculations to malaria, has studied the curve in epidemics, relating their course to the density and longevity of anophelines, the anthropophilic index and to the length of the extrinsic cycle. He discusses variations in incidence other than annual variations. These are periodic, long-term, or irregular. The point is made that very small changes in the essential transmission factors can cause long-term variations.

There is also a possibility of local extinction of the disease as a result of minor changes and of husbandry. Non-periodic outbreaks occur within the

distribution of highly anthropophilic vectors, but are usually due to gross causes or occur on the margins of their distribution.

There are four species of malaria parasites in man. They are intracorpuseular parasites belonging to the genus *Plasmodium*. They are respectively: *P. vivax*, *P. ovale*, *P. malariae* and *P. falciparum*. The reader is referred to the appendix, pp. 884-902, for the life history and other details. (Table I, p. 38.)

ÆTIOLOGY OF MALARIA (PLATES II AND III, PP. 70, 71)

The species of parasite causing malaria in man differ from each other in morphology, but the general course of their life-history is similar. They all have two distinct phases: intracorporeal and extracorporeal. Each species has its special intracorporeal erythrocytic life-cycle that may last approximately 48 to 72 hours. It was estimated by Ross that at least 150 million malaria parasites must be present in the peripheral blood before an attack of fever is produced. The extracorporeal stage is undergone in the body cavity of an anopheles mosquito.

The malarial parasite can be recognized in fresh unstained malarial blood an hour or so before a paroxysm; it is a pale disc inside the red

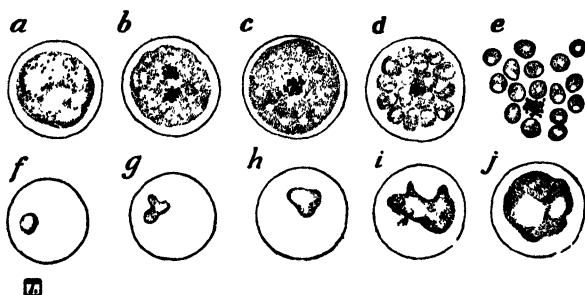


Fig. 4.—Evolution of the tertian parasite, unstained.

blood corpuscle (Fig. 4, a), and at a later stage a number of fine black or reddish-black particles of pigment (*hæmozoin*, formerly known as *melanin*) are scattered throughout its protoplasm. This pigment is believed to be the excrement of the parasite. It collects, as the parasite grows, in central blocks round which the protoplasm becomes divided into segments (merozoites) (Fig. 4, d); when the cycle is complete the containing corpuscle (host cell) breaks down and liberates the merozoites, none of which contain hæmozoin. This stage coincides with a clinical fever.

A number of these freed merozoites escape phagocytosis by wandering leucocytes and attach themselves to other red corpuscles, enter them, and grow at the expense of the hæmoglobin, exhibiting active amœboid movements. When appropriately stained, the free merozoites are seen to consist of a nucleus surrounded by a ring of protoplasm; as they reach maturity a nucleolus becomes visible (Fig. 5, a, j). In the pre-sporulation phase the nuclear elements become scattered throughout the protoplasm, and around them the segmenting parasite arranges itself to form merozoites (Fig. 5, b, c). The vesicular character of the nucleus does not

become apparent in the merozoites until they lie free in the plasma. The hæmozoin, or pigment particles of the malaria parasite, are either black or dark brown dust-like specks, grains or rods, isolated or aggregated into more or less dense clumps. As long as the nucleus remains entire, the hæmozoin is peripheral, but when segmentation takes place it becomes central.

The *extracorporeal* or *mosquito stage* commences with a process of ex-flagellation. This is a sexual phase which can take place in the blood

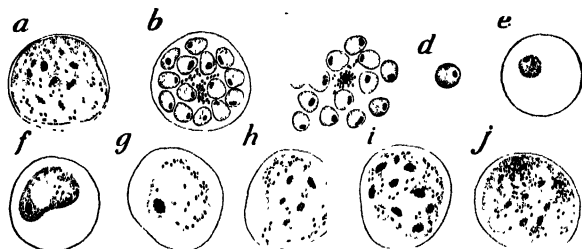


Fig. 5.—Evolution of the tertian parasite, stained.

after it has been withdrawn from the body. As observed in fresh wet preparations of blood the flagellated body is derived from the male sexual cells or gametocytes, which are composed of protoplasm and hæmozoin and which possess, on more minute examination, a distinctive structure. These sexual cells are usually round, but in subtertian malaria (*P. falciparum*) they are crescentic. These well-known "crescents" become rounded off before flagellation. The flagella (more correctly, the microgametes) number from one to six or more. They are extremely delicate filaments, which move about rapidly and which every now and

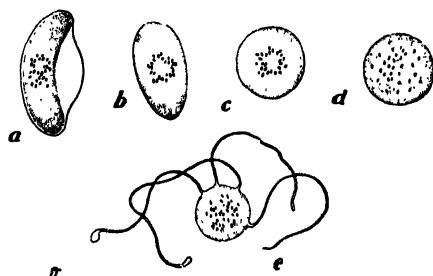


Fig. 6.—Evolution of the flagellated body from the crescent (male gametocyte).

again break away and swim about with vibratile movement (Fig. 6). Only the male cell (microgametocyte) undergoes this process: the female (macrogametocyte) remains rounded and stationary until fertilized by one of the erupted flagella (microgametes). This event signalizes the first stage in the development of the malaria parasite in the stomach cavity of the anopheles mosquito. There sporozoites develop in the oöcyst on the stomach of the mosquito and later migrate to the salivary glands of this

insect, gaining entrance to the blood-stream of man via the saliva. They then penetrate the hepatic cells where the pre-erythrocytic and exo-erythrocytic cycles take place for seven days or longer.

The tissue cycles of the malaria parasites have now been proved to take place in the hepatic cells (in *P. vivax*, *P. ovale* and *P. falciparum*). The primary protozoal mass in the liver is known as a *cryptoschizont*, which divides later into *cryptomerozoites*. There are thus four distinct cycles of development—the *pre-erythrocytic*, the *exo-erythrocytic* in the liver cells, the *erythrocytic* in the red blood corpuscles, and the *sexual* commencing with the growth of gametocytes in the blood and continuing with *sporogony* in the tissues of the mosquito. (For full details see p. 895.)

Suppression of malaria by milk.—In connection with the nutritional needs of the malaria parasites, Maegraith and colleagues (1953) have made the somewhat remarkable discovery that a diet of milk and vitamins renders rats resistant to malaria parasites (*P. berghei*). Hawking has found that P.A.B. (*P-aminobenzoic acid*) is an essential metabolite for *P. berghei* and is absent from milk.

This furnishes a partial explanation for the fact that human infants in the first 3–4 months of life seldom suffer from malarial infections, other factors being greater inaccessibility to the mosquito and a smaller surface area.

Transmission of malaria by blood transfusion, drug addiction and salvarsan injections.—There is risk of conveying malaria in the transfusion of citrated or stored blood; *P. vivax* especially may be found in the blood of donors exposed to infection within three years before the transfusion. In London a case of fatal quartan malaria has been recorded in a baby transfused with compatible blood from its father who had lived in Ceylon twelve years previously and who had never suffered from any clinical manifestations of malaria (Nabarro and Edward). Gardner and Dexter have recorded a similar instance in which the interval was seventeen years. There have been several instances of transmission of quartan with blood refrigerated for four days (Rogers, 1947). Boventer has found *P. vivax* viable for 13 and *P. falciparum* for 21 days.

In non-malarial countries persons who have had malaria should not be used as blood donors. In malarial countries this rule cannot apply. If fresh blood must be used, the recipient should be given chloroquine, paludrine or atabrin as a prophylactic, and the risks of transmission are reduced if the donor has taken antimalarials regularly. Dried plasma and serum prepared from malarial blood are safe.

Hutton and Shute demonstrated that malaria parasites may survive for days, or even weeks, in blood stored at low temperatures—about 4° C.

In Cairo, severe, and even fatal, subtertian malaria was recorded by Biggam in heroin drug addicts from indiscriminate use of unsterilized syringes containing congealed blood. Similar instances have been recorded in New York. Helsen discovered 49 cases, of which 27 died.

Similarly, virulent subtertian malaria may be transmitted by unsterilized needles in intravenous injections of salvarsan, as recorded by Wenyon (1918) and Black (1939). An accidental infection from autopsy is recorded by Holm (1946).

TABLE I

TABULAR STATEMENT OF THE CHARACTERS OF THE FOUR SPECIES OF MALARIA PARASITE

	Duration of schizogonic cycle	Move-ment	Hæmoglobin	Trophozoites	Adult schizont	Number of merozoites	Form of gametocytes	Alterations in corpuscles	Relative number of parasites in peripheral and visceral blood	Liability to relapse
1. Benign tertian parasite, <i>Plasmodium vivax</i> .	48 hours	Active anæmobic.	Fine, yellowish brown.	Signet rings of various sizes; growing forms irregular in size, with vacuole.	Larger than a red cell.	14-24 average 18-20.	Round or slightly ovoid larger than the red cell.	Hypertrophied and pale stippled with Schüffner's dots.	Parasites numerous in all parts of the body in various stages of their cycle.	Relapses noted up to 3 years from time of original infection.
2. Quartan parasite, <i>Plasmodium malariae</i> .	72 hours	Slight, in immature forms.	Coarse, and dark brown.	Signet rings, as in <i>P. vivax</i> ; growing forms band-like or angular. Vacuole soon disappears.	Slightly smaller than a red cell.	6-12, average 8.	Round or slightly oval, size of red cell.	Not enlarged, may be slightly contracted; no Schüffner's dots, but sometimes fine stippling.	As in <i>P. vivax</i> .	Infection particularly persistent. Relapses may occur for 10-21 years or more from time of original infection.
3. Subtertian parasite, <i>Plasmodium falciparum</i> (<i>Laverania malariae</i>).	24-48 hours (irregular)	Active anæmobic.	Pigment blacker than in other forms; may be aggregated into coarse granules.	Rings small often containing two clear nuclei, and sometimes attached to edges of red cell. Smaller in acute; larger in chronic stage.	Distinctly smaller than a red cell.	8-32 sometimes more variable.	Crescentic or sausage-shaped.	Usually unaltered; in later stages paler, sometimes containing coarse dots or irregular mottling (Mauve's spots or clefts)	The chief development of the parasite takes place in the internal organs; hence the relative scarcity of all, save most immature forms, in peripheral blood.	Much less than in other two forms; infection intense in early stages. Relapses rarely occur after 9 months from time of infection. Maximum period observed, 1½ years.*
4. "Ovale" tertian parasite, <i>Plasmodium ovale</i> .	48 hours	Non-anæmobic.	Blackish brown.	Rings indistinguishable from those of <i>P. malariae</i> .	Smaller than a red cell.	8-12	Oval, size of red cell.	Oval, slightly enlarged and irregular. Stippling and fibrillated margin.	As in <i>P. vivax</i> .	Short-lived infection as a rule; may persist for 1½ years.

* Walters and Shute (1960) have drawn attention to quiescent infections in symptomless Nigerians lasting 19 months and longer in England.

Transmission of malaria to the foetus.—Possibly the infection takes place by a mechanical tear, or placental hæmorrhage, by which the parasites gain entrance to the foetal blood. Lopatin suggested intra-uterine emigration of infected maternal erythrocytes into the foetus as a result of damage to the maternal blood vessels. Congenital malaria has long been known in Turkey as “gigli sitma”—hidden or secret malaria.

This may be due to small infarcts or capillary lesions, or to pathological changes in the placenta as a whole as the result of overwhelming malaria infection. Thus Blacklock and Gordon in Sierra Leone found malaria parasites (*P. falciparum*) in the maternal blood spaces in 88 per cent. of parturient women, yet in not a single instance could they be demonstrated in the foetal blood; though of children born of mothers with infected placentæ one quarter died within one week after birth.

Congenital Malaria.—Premature placental separation is suggested by the case of Tanner and Hewlett (1935) as occurring in the second of binovular twins. The commonest form is benign tertian (*P. vivax*) ranging from 16 days to 2 months after birth (Brown, 1924, Gammie, 1944). Subtertian parasites have been found in the blood of a premature child by Buckingham and crescents of *P. falciparum* in the blood of an infant of seven days (Heiser) and an undoubted case by Dimson, 1907. Others have been reported from Paris (Bindeau) and Italy (Pozzioli). In Ceylon transplacental infection of the foetus appears to be comparatively frequent (Wickramasuriya). *Plasmodium ovale* behaves like *P. vivax* and a congenital case has been reported by Jenkins (1957).

Morbid anatomy and pathology of malaria.—The pathology of malaria is based upon subtertian infections (*P. falciparum*). Lesions in the internal organs are due to the invasion and distribution of the infected red blood corpuscles with consequent loss of oxygen carried to the tissues. The changes in the vascular flow within the organs result from systemic disturbances, such as vascular collapse, obstruction of small vessels by auto-agglutination, thrombosis, infarction and similar effects due to clumping together of parasitized red cells. All these factors tend to slow down the circulation and cause “sludging” (Knisely). This is thought to be due mainly to the production of a fibrin-like substance. Cardiac and vascular failure (medical shock) result from these changes. There are, moreover, explosive discharges of protein from liberated merozoites and disintegrated products of red cells, destroyed parasites and extrusion of pigment.

Spleen.—The spleen, when grossly enlarged, is popularly known as the “ague cake.” Although it fluctuates in size it is most certainly *always* swollen during an acute attack. The surface is dark, sometimes almost black and, on section, dark-red, purple or chocolate-black from congestion and pigmentation. In subtertian infections the parenchyma is so softened as to be almost diffuent, the capsule being tightly stretched. The pulp is so tarry that it can be washed away by a gentle stream of water; it is diffuent and the Malpighian bodies appear pale grey. In chronic cases perisplenitis may develop from stretching or tearing of the

MALARIA

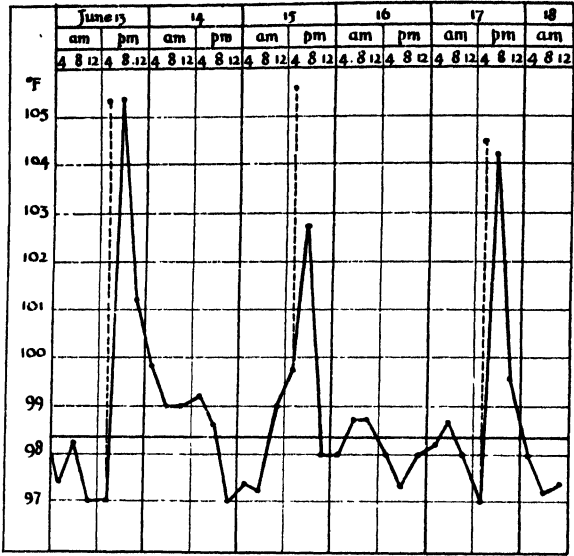


Chart 1.—Benign tertian ague.

Broken lines indicate rigors.

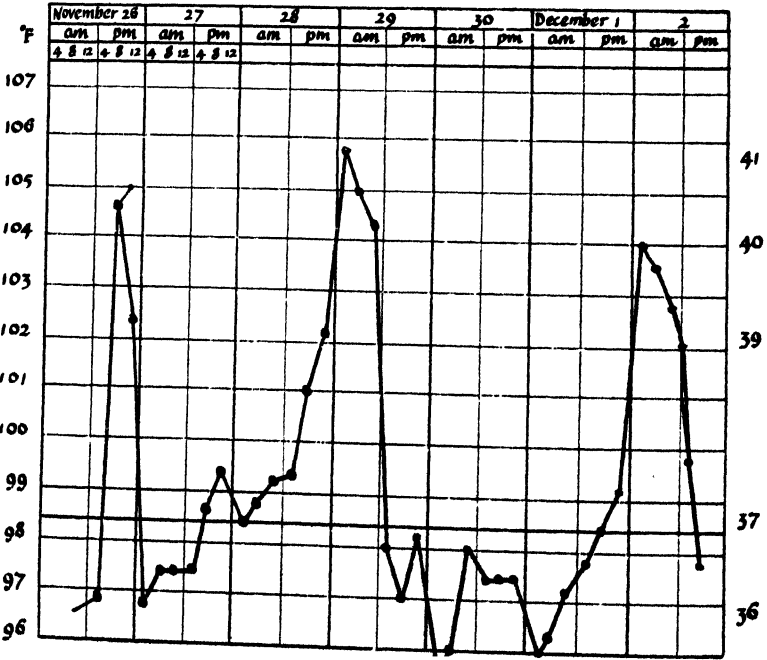


Chart 2.—Quartan ague.

capsule which may then easily rupture spontaneously or from violence. Crawford (1902) collected records of 173 cases of rupture of the spleen from 3,884 autopsies in Bengal which gave a percentage of 4·45. Its weight varies enormously according to the duration and intensity of infection. The spleen contains a large number of macrophage cells, including the cells of Billroth, cords and sinus-lining littoral cells. Clark estimated the normal spleen in Negroes at 140–160 grm. (5–6 oz.) and decided that it must exceed 300 grm. (11 oz.) before it can be reasonably detected by palpation during life. In the chronic stage there is fibrous replacement. The Malpighian bodies diminish in size, standing out as pale spots against the dark background, and the pigment becomes scattered throughout the organ. They are free from malaria parasites.

Microscopic appearances.—All stages of the parasites can be found in the red cells (in subtertian as well as in benign) and merozoites free in the pulp, but there are more parasites in the spleen than in any other organ. Malaria pigment is free in the tissue spaces and within the reticulo-endothelium, and especially in the mononuclear cells. Other blood pigments are present, but there is none in the Malpighian bodies. In acute cases the reticuloendothelial system is blocked with pigment and in the later stages this is replaced by fibrosis which may obstruct the flow of blood, whilst areas of thrombosis and hæmorrhagic necrosis occur. The venous sinuses are dilated and parasitized cells in the capillaries tend to adhere to the endothelial cells and thus increase the blockage of the lumen.

Liver.—The liver is usually congested, enlarged, pigmented and olive-brown, especially in the left lobe which receives the splenic blood. Glisson's capsule, surrounding the portal system, is stretched. In chronic malaria there is some fibrosis and round-cell infiltration originating, it is thought, from the cryptozoic stages of the parasites (*see* p. 893). The enlargement which is usually confined to the first five years of life, is mainly due to sinusoidal dilatation. Later the congestion is accompanied by involvement of the central portion of the lobule, so that it may resemble the nutmeg liver of heart failure. The slaty-grey colour is due to pigment deposits. The organ is more solid due to the increase of endothelial cells, whilst pigment is still located mainly in the outer zone of the lobules, but also in the histiocytes and connective tissue of Glisson's capsule. Parasitized erythrocytes and hæmozoïn pigment are found inside Kupffer cells.

According to modern ideas it is probable that the mild periportal fibrosis which is almost universal in African livers has a dual ætiology because, besides malaria, which irritates or sensitizes the stroma, there is malnutrition which causes diffuse, piecemeal necrosis of liver cells.

Microscopic appearances.—Parasites in all stages are found in the sinusoids and in the invaded red cells. The parenchyma cells do not usually take up malaria pigment, but the products of the destruction—hæmosiderin and bilirubin. Overactivity, following lysis of red cells, leads to obstruction and over-distension of the bile canaliculi which are frequently found stuffed with bile pigment. The Kupffer cells of the reticulo-endothelium contain hæmozoïn and become hypertrophied,

obstructing the blood flow. The parenchyma cells show all stages of degeneration and in severe cases of acute *falciparum* malaria widespread areas of focal necrosis around the central vein. Usually the cells show cloudy swelling with granular contents and diffusely-staining nuclei. Small hæmorrhagic areas may also be present. Sometimes also congestion results from right heart failure.

Malaria pigments.—Hæmosiderin contains ionizable iron, "hæmozoin". Malaria pigment (a compound of hæmatin) contains non-ionizable iron, so that the former does not give the Prussian blue reaction with potassium ferrocyanide, unless first acted upon by nitric acid and hydrogen peroxide. Its iron content is not available for resynthesis of hæmoglobin, as is that of hæmosiderin.

Kidneys.—Albuminuria is common in malaria, may indicate more than a simple "febrile albuminuria," and may presage serious kidney damage. This is specially the case in subtertian and quartan infections. Sometimes there is actual azotæmia with rise of blood pressure and cardiac hypertrophy.

In more severe cases the lumen of the tubules is filled with granular casts and fatty changes which resemble parenchymatous degeneration. Signs of glomerulonephritis are sometimes present which accounts for the rarity of azotæmic symptoms. Surbek (1931) in "quartan nephrosis" found occasionally the enlarged pale white kidneys of degenerative parenchymatous nephrosis.

Heart.—The changes found in subtertian malaria are œdema due to cardio-vascular failure, "phanerosis"—increase of visible fat in the form of droplets—without increase of the total fat. Sometimes there is also necrosis.

Bone marrow.—The yellow and adipose tissue are very vascular; the red marrow is chocolate brown, especially at the periphery, due to deposits of pigment. Phagocytosis occurs with pigment containing macrophages and parasitized cells are present in large numbers, especially immature crescents. In chronic cases the reticuloendothelium is hypertrophied.

In the bone marrow there is normoblastic response; occasionally megaloblasts may be seen and reticulocytes are increased in the peripheral blood.

Pancreas.—Often there is focal necrosis, affecting especially the nutrient vessels of the Islets of Langerhans. Rarely the picture of acute hæmorrhagic pancreatitis may be produced.

Suprarenals.—Are specially attacked in subtertian infections. This results in partial or complete loss of the yellow colour (lipoids) of the cortex, congestion and blockage of vessels with parasites, which is held responsible for algid symptoms.

Placenta.—The maternal sinuses are packed with parasites, so that nutrition of the fœtus is interfered with. Inoculation with malaria may occur at birth (possibly through the umbilical cord or placental tear).

Stomach and gastro-intestinal tract.—The mucosa is coated with mucus and there is gastro-intestinal catarrh. Therefore, achlorhydria is common in the acute stage of malaria, and this may account for the dyspepsia and gastro-intestinal irritation. The blood capillaries are loaded

with parasites, and degenerated areas of mucous membrane are encountered which may give rise to dysenteric symptoms.

Central nervous system.—The brain has a leaden hue due to deposition of malaria pigment and parasitized cells in the capillaries. Often there are punctiform hæmorrhages in the subcortical zones, especially in the corpus callosum. On the whole, the grey matter is smoky grey while the white matter is speckled with punctiform hæmorrhages (cerebral purpura). The smaller capillaries become completely blocked with parasitized cells adhering to the endothelium. The plugging is most common at the bifurcation of the blood vessels (Ariete). In areas where

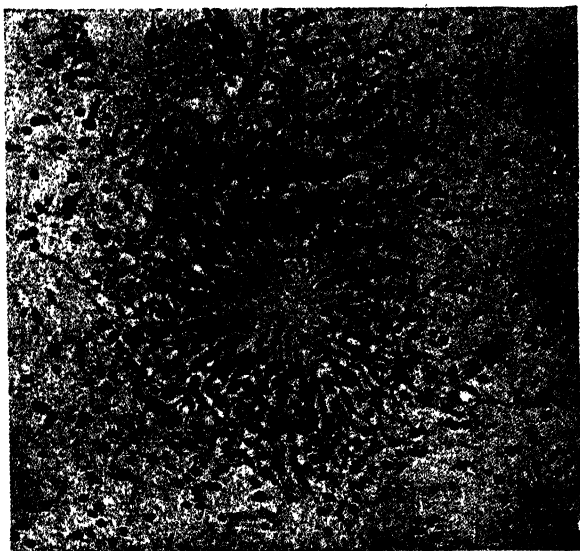


Fig. 7.—Malarial granuloma. Brain section showing plugging of capillaries of cortex and proliferation of glial cells. (*Dürk-Archiv für Schiffs- und Tropenhygiene.*)

there are actual hæmorrhages, macrophage cells abound, but the extravasated cells do not contain parasites. "Malarial granulomata" are focal degenerations in the brain substance, the result of hæmorrhages. Granuloma is really an incorrect term, for these lesions somewhat resemble tubercles and are formed by an agglomeration of glial cells around a central focus of degeneration (Fig. 7).

Three types of cerebral malaria can be distinguished on pathological grounds.

(1) *Massive infection.*—The capillaries are blocked and thrombosed. As Maegraith has pointed out, thrombosis takes place only in fatal cases. In the clinical state the vascular condition in the brain is explained by "sludging." There are numerous small hæmorrhages with "granulomata" in the subcortical zones. Clinically there is a gradual onset of mental disturbance ending in coma.

(2) *Generalized toxæmia*.—This is characterized by fits and convulsions. There are scattered small hæmorrhages. Quinine and other drugs have no effect and may actually increase toxicity by massive destruction of the parasites.

(3) *Embolism*.—Emboli produce punctiform hæmorrhages, especially in the corpus callosum.

Clinical pathology.—The loss of parasitized cells resulting from sporulation is governed by the degree of infection of the red cells, being most severe in subtertian and least in quartan.

There is also lysis of non-parasitized cells, but this does not appear to be due to any known circulating hæmolysin or to fragility in saline, but the cells in malaria and blackwater are sensitive to lysolecithin systems, suggesting some alteration in their surface properties.

Autoagglutination—an increase in α and β agglutinins—may play a part in hæmolysis. At the time of sporulation oxyhæmoglobin and methæmoglobin are thrown into the circulation as a result of red-cell destruction. Under ordinary circumstances such pigments are absorbed by the reticulo-endothelial system, but when lysis is extreme, these pigments may be thrown into the urine. In severe cases a combination of albumin and hæmatin may be formed which does not pass through the kidneys and is known as methæmalbumin. In established anæmia the blood cells show polychromasia, basophilia, poikilocytosis, and anisocytosis. In severe cases normoblasts and sometimes megaloblasts are seen. Basophilic stippling persists after disappearance of malaria parasites and may be regarded as evidence of persisting malaria infection. Megaloblastic changes have been reported in the bone marrow. Reticulocytosis occurs in the bone marrow and less so in the peripheral blood, especially after institution of specific therapy. Autoagglutination in subtertian malaria may be related to the "stickiness" of the *parasitized* red cells. Complement fixation bodies exist and can be shown by using antigens prepared from the spleen or from suspensions of malaria parasites.

Leucocytes.—There is frequently a leucopenia associated with increase of the large mononuclear cells, but this leucopenia is not characteristic of malaria. Some may show a leucocytosis, especially when there is some secondary infection, such as pneumonia and this possibility must be borne in mind. The white cells frequently contain malarial pigment which is usually found in the monocytes, lymphocytes, but sometimes in the polymorphs, even in eosinophiles. Such pigment-containing leucocytes are indicative of a very recent infection.

CHEMICAL CHANGES IN THE BLOOD

Blood proteins.—The reduction in total plasma protein is mainly due to reduction in albumin and there is usually an increase in globulin. The albumin-globulin ratio is therefore altered. Therapeutic malaria is followed by a return of protein to normal in a process which takes three weeks. These changes are not due to the fever alone, but are associated with upset of liver function which occurs in malaria.

Cholesterol and lecithin.—There is hypo-cholesterolæmia during malaria, but it may rise during the rigor and fall to subnormal in the apyrexial

periods, so that further investigation of lecithin-changes may shed light on the mechanism of hæmolysis.

Blood sugar.—As glucose is essential for the respiration of plasmodia changes in the blood sugar are to be expected. Sinton reported a rise in blood sugar during pyrexia in both *P. vivax* and *P. falciparum*. It is suggested that this rise may be associated with change in liver or adrenal function.

Inorganic elements.—Plasma potassium is raised in febrile persons and is at its height during segmentation, but in low grade or chronic malaria there may be no change. The rise of potassium in acute malaria is probably due to destruction of red cells.

Physical changes.—The E.S.R. is increased in malaria and is restored to normal after treatment. The degree is dependent upon the protein content of the plasma and the activity of the surface of the cells. The fall of protein in the blood may be such that the permeability of the vessels is affected and the osmotic pressure of the plasma reduced.

pH and alkali reserve.—As parasites use glucose for respiration it is possible that pyruvate and lactate may accumulate under conditions of anoxia, such accumulation would result in a fall of pH and loss of alkali reserve. Acidosis is exceptional.

Polycholia.—Up to a certain point in pathological hæmoglobinæmia the liver is capable of dealing with liberated hæmoglobin, so that, when this pigment is set free in the blood, serum secretion and flow of bile (bilirubin) are correspondingly increased.

Liver function in malaria.—Clinical signs of liver dysfunction have been recorded in all forms of naturally-acquired malaria, as well as in the therapeutic induced disease, but they are most pronounced in certain forms of *P. falciparum*. Enlargement of the liver following the paroxysm is comparatively common.

Lichtman (1942) has described six cases of extensive hepatic necrosis. In course of review of 1,153 cases Kern and Norris (1944) reported 59 had enlarged livers, abnormal Van den Bergh reactions and raised serum bilirubin. The results of bromsulphthalein retention tests were in accordance with other abnormal findings. Kleeberg and Birnbaum (1947) have investigated the Weltman reaction in *P. vivax* and *P. falciparum* malaria. This reaction measures the coagulability of the patient's serum in solutions of calcium chloride which is governed by the globulin content. There is a close relation between the changes in the coagulation of the serum in lower calcium concentrations and in the sensitivity of the erythrocytes to lysis in bile solution indicating hepatic damage.

Dole and Emerson (1945) find that during the malarial attack the total proteins of the serum remain within normal limits, but the albumin/globulin ratio is depressed.

Bile is not found in the urine unless there is frank clinical jaundice. Urobilin and urobilinogen excretion has been fully investigated by Kingsbury (1925). He found that it did increase in malaria, especially in subtertian, but it is not of absolute diagnostic value.

The prothrombin content of the blood is not changed in the febrile period because there is thrombocytopenia, as reported by Maslova (1942) who

found decrease in blood platelets and lessening of coagulation time during a malarial rigor. It is therefore clear that deviations in the so-called hepatic function tests occur in both naturally-acquired and therapeutic malaria.

THE CLINICAL PICTURE

Symptoms of malaria.—An attack of malaria may either be a primary attack or a relapse. Conjunctival ecchymoses, especially at the inner canthus, have been described as an early complication of benign tertian malaria, usually between the 3rd and 7th days. These ecchymoses rapidly spread to cover the lower half of the sclera. A primary attack normally develops after an incubation period of 10–14 days, but when blood is used for inoculation, the incubation period varies from 48 hours to one month, depending upon the numbers of living parasites injected. By direct blood inoculation it is about 11 days. In insect-transmitted subtertian malaria, where the number of infecting bites is increased, the *incubation period* tends to be shorter and may only be five days, thus some artificially infected with benign tertian may show no clinical signs or exhibit parasites in the blood for as long as nine months and similar long periods are often seen in patients leaving the endemic area. This is known as *latent malaria*. The latent period preceding the primary attack is known as *incubation latency*; a period or periods following upon the primary attack are known as *infection latency*. In subtertian malaria it is possible to have a primary attack in the absence of any noticeable symptoms, but there is no latency in the same sense as in benign tertian. The type of temperature curve, whether *intermittent* or *remittent*, is less significant than formerly considered to be the case. Thus primary benign tertian infections may produce a remittent temperature curve before assuming the classical *intermittent* character. Two or more generations of tertian parasites, maturing in the blood at different times, will produce quotidian fever and two generations of quartan will give a fever on two successive days—*quartana duplex*—or conversely on three successive days, a quotidian fever—*quartana triplex*.

Relapses are defined as recurrences of malarious symptoms and the reappearance of malaria parasites in the peripheral blood, following recovery from the initial attack. Therefore relapses must be distinguished from reinfections.

Recrudescences of malaria are defined as relapses of the patient at the time he is removed from the endemic area. Relapses often follow the cessation of suppressive treatment, exposure to cold, exertion, parturition, or surgical operations. Benign tertian and quartan relapse most frequently. Reinfections do not show the remittent character of the primary attack, but assume tertian or quartan classical forms.

The characteristic *ague* is divided into three stages: (1) cold stage, (2) hot stage and (3) sweating stage. One or even all these stages may be absent on occasions, especially when the infection is of long standing, whilst in subtertian fever many symptoms are so bizarre that they may be most misleading, so as to enforce the conviction that in many respects it is quite a different disease.

Herpes on lips and nose (fever sores), often extensive, frequently follow the rigors and are an accompaniment of all forms of malaria. Similar eruptions have been noted on the ears.

Premonitory stage.—For several days before the actual attack the patient may be conscious of headache, lassitude, a desire to stretch or yawn, aching in the bones, anorexia, sometimes vomiting.

Cold stage.—This usually lasts one to two hours, and is the rigor, or "ague." The feeling of cold is intense and universal. The teeth chatter; the patient shivers from head to foot and wraps himself up in any garment he can lay his hands upon. Vomiting may be most distressing. The features are pinched, the fingers shrivelled and the skin blue like "goose-skin" (*cutis anserina*). The feeling of cold is purely subjective, because the temperature is rapidly rising. Children usually have convulsive fits.

Hot stage.—The hot stage may last from three to four hours. The shivering abates and gives place to, or alternates with, sensations of great heat. The clothes are thrown off. The face is flushed; pulse full, bounding and usually dicrotic; headache intense; vomiting usual; respiration hurried; skin dry and burning; the temperature rising to 104°, sometimes 106° F., rarely higher.

Sweating stage.—This usually lasts from two to four hours. The patient breaks out into profuse perspiration with sweat literally running off him in streams, saturating clothes and bedding. With sweating the fever rapidly declines. Headache, thirst and distress give place to a feeling of relief and tranquillity. When it has ceased the patient may feel exhausted, but quite well and able to go about. The body temperature is now subnormal and remains so until the approach of the next paroxysm, one or two days later. The total duration of the fever cycle may be from six to ten hours.

Urine and faeces in ague.—During the cold stage the urine is abundant, limpid and micturition frequent; during the hot sweating stages it is scanty, cloudy, sometimes albuminous. Urea excretion is increased during the rigor and hot stages, and so is that of the chlorides and sulphates. Phosphates, on the contrary, diminished during the rigor and hot stages, are increased during defervescence. Augmentation in urea excretion commences several hours before the attack, attains its maximum towards the end of the rigor, and decreases during the terminal stages, though still above the normal figure.

A fleeting glycosuria has also been observed from time to time. The urine usually contains urobilinogen and urobilin in excess during the attack, but they decline with the temperature and form a valuable diagnostic sign, especially in subtertian malaria. The corresponding pigment in the faeces (*hydrobilirubin*) is increased twenty times the normal amount whilst parasites persist in the blood.

The spleen during ague.—The spleen is enlarged and painful during the rigor, but in early infections not always palpable. This has been specially noticeable in the second World War in India and Burma and the statement applies to benign as well as subtertian infections. At

first the enlargement recedes during the interval, but it tends to become chronic if relapses or re-infections are numerous, especially when associated with pronounced cachexia. This does not constitute the whole explanation; in primary cases the spleen is very soft and spongy, therefore difficult to palpate. In relapses it becomes harder and more fibrous. Sometimes when a patient is in bed the spleen remains soft, but becomes harder when he gets up. Spontaneous and fatal rupture may occur in benign tertian as well as in subtertian infections, more usually as a result of direct violence (de Saram and Townsend, 1943). A successful splenectomy does not, as has often been stated, extirpate the malarial infection.

Hennessy and others have recorded that splenic rupture, through causing severe internal hæmorrhage, may produce misleading symptoms which may mimic those of rupture of the bladder by causing urinary irritability and hypogastric pain. There is often a latent period with absence of symptoms (Fry). Referred pain to the tip of the left shoulder is known as Kehr's sign. In the early stages it is present in a small proportion of cases. Galloway noted that a pain moving from the uppermost shoulder to the one on which the patient is recumbent is a marked feature. Changes in the left lung base may serve as an aid to diagnosis. The histopathology of these friable spleens (Lubitz) shows that a subcapsular hæmatoma precedes rupture and leads to capsular tear. In acute malaria small hæmorrhages occur in the vicinity of the capsule or deep in the tissues. There is diffuse cellular hyperplasia, with dilated sinuses, and occasional thrombosis and infarction.

Spontaneous rupture of the chronically enlarged spleen is very rare. It is, however, found in acute malaria in a primary attack. It is more common in therapeutic malaria, having regard to the age of the patient and the entire lack of immunity. It is more frequent in *falciparum* malaria, but has been recorded with *P. vivax* as well. Splenic rupture has been recorded in twenty-one military personnel, four in the first World War, the remainder in the second and in Korea. Crawford (1902) collected records in India of 173 cases from 3,884 autopsies in Bengal—a percentage of 4.45. (Splenic rupture has been recorded also in portal thrombosis, torsion of the splenic pedicle, in kala azar, acute infective hepatitis, bacterial endocarditis, splenic abscess, leukaemia, erythroblastosis foetalis, and aneurysm of the splenic artery (Covell)). In operations on the spleen massive fluid replacement is always necessary.

An important lesson for clinicians is that failure to palpate the spleen should not justify omission of microscopic blood examination for malaria parasites.

Period of the day at which ague commences.—Quite a large proportion of agues "come off" between midnight and noon or in the early afternoon. This time factor may constitute an important point in diagnosis, especially as pyrexial attacks somewhat simulating malarial agues may be caused by liver abscess, tuberculosis, *Bact. coli* infections of the urinary tract and septic conditions, in all of which febrile recurrences are apt to take place during the afternoons or evenings.

Course of benign tertian and quartan fevers.—Benign tertian ague usually lasts ten hours or less and may be taken as the type of a malarial attack. In some cases the rise of fever is rapid and high, and the temperature may reach 105° to 106° F. within an hour or so; on the

other hand, in some cases none of the clinical phenomena are present and the temperature does not rise above 99–100° F. Benign tertian, unless complicated, is not usually fatal; but the persistent and relapsing character makes it a tiresome disease and, if prolonged, may produce severe anemia and debility.

Certainly many strains of *P. vivax* seem to exist which differ in their virulence; some are mild, as in Holland; sometimes the fever is trivial and isolated attacks, without recurrence, are common enough. Various strains of *P. vivax* have been found to possess distinctive characters and vary in the number and frequency of the relapses they produce; for instance, the virulent New Guinea strains of Fairley and the "Chesson" strain of American workers which tends to relapse every six weeks, may be compared with the "benign" St. Elizabeth strain from America and the Madagascar Horton strain which may not relapse for several months.

The presence of a rigor appears to be an index of severity. The mean maximum temperature for the paroxysms is 104.2° F. As a general rule, the duration of a simple benign tertian infection before the parasites die out from the peripheral blood is nine months to one year after leaving the endemic area, but exceptions to this rule occur, as clinical relapses, with parasites in the blood, have been recorded as long as three years after the original infection. As it is seldom fatal the pathology is not so well-known as that of subtertian malaria, but it resembles it in a minor degree.

In the endemic areas the quartan parasite is most frequently found in children.

The fever in *quartan* malaria is generally smart while it lasts, and is well-defined in its various stages, but it does not produce much systemic disturbance or cachexia or rigors. It has often been remarked that, whilst individual attacks of this infection are amenable to quinine and atabrin, the disease is more persistent than tertian or subtertian, so that attacks are apt to occur from time to time over a period of many years and may persist as long as 12–21, and in one authentic instance after 45 years (Lentini, 1956). It is becoming increasingly realized that sometimes quartan parasites may be present in the blood without evoking any special symptoms. Parasites are usually scarce in the peripheral blood. They are more resistant to anti-malarial drugs in the sense that they persist in the bloodstream for a week or more while the patient is taking the drug.

Quartan periodicity is the hall-mark of quartan malaria and is hardly ever found in any other disease. Double quartan and triple quartan fevers may be observed. In the latter the temperature course becomes quotidian. Occasionally, quartan fevers are encountered without splenomegaly and apparently when parasites can be found in the blood only after prolonged search: sometimes not at all, so that their true nature can be ascertained solely by the action of quinine or chloroquine by injection.

Quartan malaria nephrosis.—Although kidney changes are associated with subtertian malaria, nephrosis is commonest in countries where the quartan parasite predominates.

According to Giglioli both sexes are susceptible, and especially children, in whom quartan malaria is most common, but in adults males predominate. He regarded albuminuria in a febrile attack as an indication of parenchymatous nephritis; Goldie, on the other hand, took a less serious view and considered the pathological picture as one of nephrosis and due to the production of malarial toxins over a long period. The special liability in quartan is to be ascribed to insufficient initial treatment on account of the all too frequent non-recognition of this infection due to its mild character. It is thus much more liable to relapse into the chronic stage. The nephrosis declares itself by generalized oedema and the passage of decreased urine containing albumin and casts. The blood urea is not necessarily raised.

Course of ovale tertian malaria.—This type closely resembles the benign tertian in its periodicity; but, generally speaking, the attacks are sudden, short and mild, and not accompanied by any grave degree of anæmia, whilst the rigors are more apt to take place during the evenings. Rheumatic-like pains in various parts of the body, especially the lumbar region, are characteristic, and sometimes pain referred to the appendix may suggest appendicitis. There is usually no excess of urobilinogen in the urine. Occasionally severe infections are encountered, as related by Garnham (1955), with rigors, a temperature of 105° F. (40.6 C.), irregular tertian periodicity and persistent headache. It may evince considerable latency. The Donaldson strain from the Philippines differs in several respects from the Liberian: in the latter the parasites are larger and the number of merozoites fewer.

Course of subtertian or malignant malaria.—There are probably many strains of *P. falciparum* differing from one another in virulence as James has shown with his Sardinian strain. Herpes labialis is commoner with this form.

In distinguishing subtertian malaria the *rigor stage* is relatively less marked, or may be absent entirely. The primary attack begins with a sense of chilliness. The hot and sweating stages are more prolonged and liable to be followed by an adynamic condition (see p. 73), together with vomiting, intestinal irritation, bone pains, anorexia, headache and supra-orbital neuralgia and a degree of moderate sweating. After apparent recovery from fever there is a tendency to recrudescence at shorter intervals than in benign tertian. Subtertian fevers are accompanied by rapid hæmolysis, toxæmia and succeeded by marked cachexia. The underlying pathology is due to the sporulation of parasites in the internal capillaries and relative blood-stasis owing to the stickiness of the infected red cells which tend to agglomerate and also to iso-agglutinins in the serum, so that, at any time during the course, and especially in primary infections, symptoms of the gravest character may appear. The tendency for successive paroxysms to overlap, or to become *subintransit*, is marked. When intermissions are distinct the crisis is what is called "*a double crisis*." Thus, when the fever has attained its apparent fastigium, there is a drop of one or more degrees of temperature—a *false crisis*—followed by a fresh rise which is then succeeded by a *true crisis*. This peculiar phenomenon has been attributed to the presence of two generations of parasites in the blood, one of which matures somewhat later than the other; it occurs ordinarily

in one other tropical fever: kala-azar (Chart 3). Such an infection may therefore produce a quotidian typhoid-like temperature chart (Chart 4). Even at this stage the temperature may not exceed 103° F. or 104° F. (39.4° – 40° C.). The liver is usually enlarged and tender, especially in the

7th day

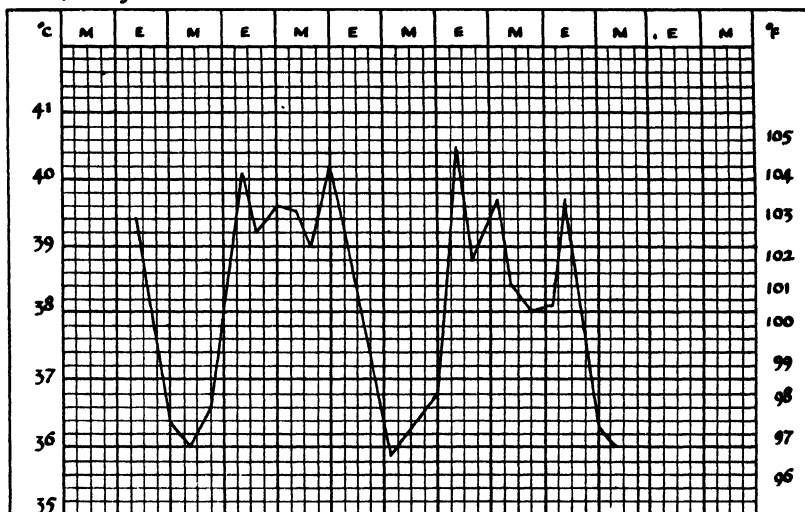


Chart 3.—Subtertian fever (*P. falciparum*).

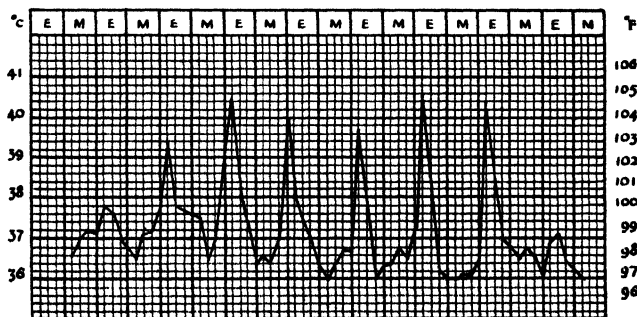


Chart 4.—Quotidian fever (two generations of *P. falciparum*).

region of the gall-bladder which itself is generally swollen and turgid with bile, as the result of extensive hæmolysis. These phenomena may give rise to the impression of gall-bladder disease.

Though this fever may be justly regarded as dangerous to life, yet it is singular that subtertian parasites may exist in the blood for months without seriously interfering with health. Sometimes attention is drawn in other directions—to cedema of legs, diarrhoea, dyspepsia or some other

apparently small complaint, quite unconnected with malaria—and these may appear in men returning from West Africa in whom the first symptoms of ill-health may be noted after several weeks' residence in a temperate climate.

Manson said, and it is particularly apt, "What one sees in the peripheral circulation is only a reflection of the drama which is occurring in the internal circulation."

Bilious remittent.—One type of subtertian fever—bilious remittent—has long been recognized on account of the bilious vomiting, gastric distress, sometimes bilious diarrhoea, sometimes constipation, which accompany the recurring exacerbations. It is further distinguished by the pronounced icteric or, rather, reddish yellow or saffron tint of skin and sclera—a tint derived, probably, not from absorption of bile as in obstructive jaundice, but from modified hæmoglobin (serum bilirubin) free in the blood or deposited in the skin and sclerotics. Sometimes cases are seen with intense icterus, high serum bilirubin and jaundiced sclera, without splenomegaly, but with large numbers of parasites in the peripheral blood. This type may be readily mistaken for various forms of obstructive jaundice.

Pernicious attacks.—The French neatly designate these *accès pernicieux*. They characterize subtertian infections, and may supervene, in apparently mild cases and carry off the patient with horrifying suddenness—as suddenly as an attack of malignant cholera. Pernicious attacks are apt to develop in drug addicts (*see* p. 37). They are classifiable into: (1) *septicæmic* (or *toxæmic*) type, accounting for about 30 per cent., with numerous parasites in the blood, death taking place from cardiac failure; (2) *cerebral*, accounting for some 55 per cent., ending usually in coma, in which, compared with other forms, parasites are usually very scanty in the peripheral blood; (3) *algid*, with subnormal temperatures and a clinical syndrome resembling that of shock, accounting for some 14 per cent., and finally (4) *renal*, with œdema and nephritic signs which, though rare, amount to about 1 per cent. of the total.

Cerebral forms.—In the course of what seems to be an ordinary malarial attack the body-temperature, instead of stopping at 104° or 105° F., may continue to rise and, passing 107°, rapidly mount to 110° (or even, rarely, to 112°). The blood shows hyperinfection with *P. falciparum* and more than 5 per cent. of erythrocytes are infected and most contain about two parasites in each corpuscle. The patient, after a brief state of maniacal or, perhaps, muttering delirium, becomes rapidly unconscious. The pupils are dilated and the corneal reflex absent. The fundi are usually normal. The skin is hot and burning. The legs are usually spastic. Fever sores (*herpes labialis*) are often observed around the lips and mouth. There is an almost distinctive facies. The pulse is rapid and dicrotic, and there may be generalized muscular twitchings. Splenic pain may be present. At first there is a disorientation with motor aphasia. Incontinence is usually a dangerous sign. Changes in behaviour, such as insolence or insubordination, may often be encountered in the early stages, excitement, mania and coma then follow.

Coma.—Sometimes the patient, without hyperpyrexia (the temperature perhaps not rising above, or even up to, 104°), may lapse into coma. The coma may pass away with a crisis of sweating; on the other hand, an asthenic condition may set in and death supervene. There is often a paralytic squint, extensor plantar response and Cheyne-Stokes respiration. When subcortical hæmorrhages are present, death usually ensues. There is a marked increase of pressure in the cerebro-spinal fluid, with increase of lymphocytes up to 400 per c.mm., as well as of albumin and globulin. Occasionally, granules of malarial pigment may be found. It is important to note that parasites may be very scanty in the peripheral blood and not infrequently they appear to be absent altogether. The coma may persist for as long as 46 hours and then recovery ensue with quinine injections as in the case reported by A. G. Tresidder in 1914.

Marriott (1945) has classified the symptoms as follows:—

Cerebral depression.—All stages from drowsiness to deep coma.

Cerebral excitation.—All stages from mild excitement and talkativeness to extreme restlessness and mania.

Cerebellar ataxia (Sawyer-Brown variety) has been recorded, and may be a permanent sequel to cerebral malaria.

Behaviour changes—character alterations.—Irritability, and depression developing in a previously well-balanced personality. Psychotic symptoms are not uncommon.

Meningismus closely simulating meningitis and *focal nervous lesions* resulting in dysphagia, diplopia, etc. Sometimes a focal spine lesion may cause paraplegia.

Epileptiform attacks.—There has been some divergence of opinion about the origin of epilepsy following malaria. Mohr thinks that symptoms of meningitis, as the result of damage of brain substance in cerebral malaria, may arise, including epileptiform attacks.

Malarial amblyopia.—In rare instances a comatose pernicious attack ends in blindness. The amblyopia is usually transient, lasting for an hour or two only. On the other hand, it may be persistent; in which case optic neuritis, peripapillary oedema, extravasation of leucocytes, plugging of retinal and choroidal vessels by parasites or pigmented leucocytes, and consequent multiple hæmorrhages, may be found in the fundus. The disc itself is rosy or cherry-pink in colour, which is considered diagnostic. If the hæmorrhages are minute they are discoverable by the microscope only; on the other hand, large retinal hæmorrhages do occasionally occur.

Other cerebral forms.—There may be *sudden delirium* ending in coma and, perhaps, death; conditions simulating *cerebro-spinal meningitis*; *delusional insanity*; *dementia*; *acute alcoholism*; various forms of *apoplectic-like* conditions and of *paralysis*, complicated, it may be, with *aphasia*. Seizures of this description, if not fatal, may end in *permanent psychical disturbances*, with a tendency to *suicide*. Temporary debility, or even complete *loss of memory*, may succeed severe cerebral malarial infection, and cataleptic narcolepsy has been recorded. Winging of the scapula due to nerve atrophy has also been seen.

ALGID FORMS.—The algid forms of pernicious attack, as indicated by the name, are characterized by collapse, extreme coldness of the surface

of the body or, in other words, by peripheral vascular failure. These symptoms usually co-exist with elevated axillary and rectal temperature. Flooding of the peripheral blood with vast numbers of parasites in all stages of development—gametocytes as well as schizonts—is sometimes found. The prognosis is usually bad, but rarely this may be seen in an attack of average severity. It indicates a continuous fever of at least two weeks, or a relapse of short duration.

Gastric form.—This may be associated with, and in a measure be dependent on, acute catarrhal dyspeptic trouble. It is accompanied by severe epigastric distress, tender retracted abdomen, and incessant vomiting.

The choleraic form.—The stools suddenly become loose, profuse, and numerous, but generally not so profuse or colourless as the rice-water discharge which pours from the patient in true cholera; they retain a certain amount of biliary colouring, and may be mucoid, or even bloody. The high axillary temperature, if present; a history, maybe, of recent ague fits; the subsequent rapid cessation of choleraic symptoms on the appearance of the hot and sweating stages; the colour of the stools, and other collateral circumstances, usually suffice for diagnosis.

The dysenteric form.—Another form of pernicious attack is characterized by the sudden appearance of dysenteric symptoms, by severe and recurring hæmatemesis, or by hæmorrhage from the bowel or elsewhere.

The hæmorrhagic forms.—As in purpura, so in these pernicious attacks, hæmorrhages may occur in almost any organ and may be generally distributed over the body.

The œdematous form.—General anasarca with chronic subtertian malaria has been noted in debilitated subjects as, for instance, in war refugees in Greece and in the great Ceylon epidemic of 1934. Wickramasuriya recorded it in 40 per cent. of 357 cases specially investigated in pregnant native women and it was attributed to reduction of the plasma proteins.

Acute hæmolytic anæmia.—There is a rapidly developing and progressive anæmia in the fourth or fifth week of a primary subtertian attack or in an *untreated chronic relapse*, only comparable to that seen in the most advanced stages of pernicious anæmia. These cases are characterized by great pallor of mucous membranes and conjunctivæ, cardiac distress, dyspnoea, hæmic murmurs, and retinal hæmorrhages.

Rarer clinical forms of subtertian malaria.—Rare cases with rapidly developing anasarca and ascites were observed in Macedonia and in Palestine during the 1914–18 war; and œdematous forms with nephritic signs, such as blood-cells in the urine, have been noted. Disturbances in the vaso-motor mechanism, as in Raynaud's disease, have been recorded, and occasionally gangrene of the toes and fingers. Otorhinologists recognize a form which simulates mastoiditis and also frontal sinusitis. Epistaxis may be a marked feature of a malarial attack. Recurrent headaches, trigeminal and supra-orbital neuralgias are common. (It must be remembered that quinine in large doses may produce tinnitus, sensations of intra cranial pressure, and even nystagmus.)

Orchitis in the course of a malarial attack may be due to agglomeration of parasites in the testes (Mayer and Bastillo).

Mixed infections.—Double infections with *P. vivax* and *P. falciparum* are common and may give rise to some confusion, especially when the ring (or trophozoite) stages of both parasites are present in the blood at the same time. More usually *P. vivax* is superimposed upon *P. falciparum*, so that the patient runs through the average course of the latter, and when he has apparently recovered, relapses of *P. vivax* make their appearance. This late appearance, it may be after a lapse of six months or even a year, was commonly observed in soldiers infected in war zones in both 1914–1918 and in the second world war in India and Burma (1943–1945). In the endemic areas of quartan malaria—in S. Ceylon and Malaya—double infections with *P. vivax* and *P. malariae* are quite common, and in these cases the latter parasite survives longer.

Malaria in indigenous inhabitants of the Tropics.—From infancy onwards the African is exposed to repeated plasmodial infection and is in a state of premunition (p. 68). Acute malaria is in these people predominantly a disease of infants and young children in whom premunition has not yet been established. Pernicious complications, including cerebral malaria, account for a considerable proportion of deaths. Soon, however, in older children and adults living in the endemic area, a gradual acquisition of relative immunity becomes evident. The rise of temperature which heralds an attack is not accompanied by shivering and the whole illness is of a very mild character which hardly interferes with the day's work. Vomiting and sweating are usually absent. Verily it resembles a different disease.

In the great majority chronic malaria exists without giving rise to significant features, even though plasmodia may be present in blood smears. Thus the picture of chronic ill-health, so graphically displayed by the sick European under similar circumstances, is absent. Splenomegaly is almost always present and a low-grade continuous pyrexia is seldom sufficiently pronounced to interfere with the daily round, but an anaemia of a moderate hypochromic type becomes established.

Malaria in pregnancy.—Pernicious symptoms are apt to develop in pregnant women infected with *Plasmodium falciparum*. Cerebral manifestations in late pregnancy arising unexpectedly, without any previous malarial history, may cause serious diagnostic difficulties. The majority are diagnosed as eclampsia, but this diagnosis should be conditional on the exclusion of malaria, so that an epileptiform attack in pregnancy is better termed "eclamptic." A lucid interval is very likely to follow intravenous quinine therapy and is apt to lead the inexperienced physician astray.

"Latent" malaria tends to persist through pregnancy, to become active during parturition or lactation. Hypertension, that most important criterion of pregnancy toxæmia, is often noted. Greater dangers are to be expected when the disease occurs in the later than in the earlier months of pregnancy. Chronic malaria in pregnancy is prone to precipitate megaloblastic anaemia (see p. 20).

Malaria after operation.—Latent malaria is often brought out by operations and is a definite factor in retarding post-operative recovery. Parry (1946) found that wounds do not heal normally, but show a tendency to hæmorrhage. Skin grafts do not take till antimalaria treatment is

instituted. Intravenous anæsthesia tends to produce cerebral malaria in infected subjects and inhalation anæsthesia broncho-pneumonia. Bodily injury, parturition or shock, may precipitate an attack of malaria, in spite of regular antimalaria drug prophylaxis. The parasite concerned in this case is usually the benign tertian. Romiti in British Guiana recorded that from 1924-1947, 3,445 patients subjected to operation gave a history of malaria and 507 suffered from post-operative attacks. Between 1948 and 1955, during which time eradication of malaria was established, 10,748 patients were operated upon and there were only 5 post-operative attacks.

Malaria in small children.—Malaria, especially subtertian, is a much more severe disease in children than in adults, especially in native races. Benign tertian malaria frequently produces the most alarming symptoms in babies, but it is not necessarily very severe and is easily controlled; but subtertian malaria is especially likely to assume the cerebral form and should always be regarded seriously. Amongst 138 babies examined periodically from birth onwards in Nigeria the infection rates were 8 per cent., 14 per cent. and 50 per cent. respectively and nearly 100 per cent. by the end of the first year. Malaria was responsible as the cause of death in 9 per cent. of infants dying in hospital; in 13 per cent. in early childhood; in 7·4 per cent. in the younger and 3·6 per cent. in the older age groups.

McGregor and colleagues (1956) have studied the effects of heavy and repeated malarial infection in Gambian infants and children. Unprotected children (without chloroquine), once infected with malaria, were observed to grow more slowly and become more anæmic than those protected with chloroquine over the first two years. Mortality rates for protected and unprotected were 3·8 and 19·2 per cent., respectively, in the first 16 months. After which time an increasing resistance to malaria was acquired and the unprotected children made rapid growth progress. Unprotected children exhibited malarial parasitæmia with enlarged liver and spleen, but without any symptoms. Therefore in African children malaria exerts its main effects in the first two years of life.

Complications.—Subtertian malaria may complicate, or be complicated by, almost any other disease; a common and very fatal terminal event is pneumonia, either lobar or broncho-pneumonia, as was noticeable in the influenza epidemic of 1918. Enteric greatly complicates the clinical picture, as do the main forms of dysentery. Pulmonary tuberculosis is very likely to supervene in cachectic cases. Primary atypical pneumonia has been associated with epidemics of subtertian malaria in the second world war in North Africa and Italy. The symptoms are very similar and in 80 per cent. malaria was present as well as pneumonia. Noma or *cancrum oris*, frequently complicates severe subtertian malaria in small children in Turkey, whilst purpuric rashes and cloasma pigmentation of the face is relatively frequent.

BLACKWATER FEVER

Synonyms.—Malarial Hæmoglobinuria; Hæmoglobinuric Fever.

Blackwater is an acute hæmolysis of the red blood corpuscles which liberate hæmoglobin into the plasma and produce hæmoglobinuria.

There are certain points of analogy between it, paroxysmal nocturnal hæmoglobinuria, the hæmoglobinuria of snake venom poisoning, incompatible blood transfusion, sickle-cell disease, the hæmoglobinuria of crush injury, favism, and the red water fever of cattle, due to *Babesia bovis*. The hæmolysis of sulphonamide and pamaquine sensitization has also to be considered.

Blackwater is now, almost universally, regarded as an exaggerated form of subtertian malaria, but this terrible disease has in recent years become rare since the introduction of the synthetic antimalarial drugs.

The geographical distribution of blackwater closely follows that of subtertian malaria. Formerly it was very common on the West Coast of Africa from Senegal southwards, in the deltas of the Niger and Congo rivers. In America it used to occur in the S. United States and in the Guianas and the Amazon. In Europe it was found in Bulgaria, Macedonia and Greece; quite commonly in both world wars.

Sometimes it almost appeared as if blackwater fever occurred in epidemics. Probably this depended on the number of susceptible persons, especially new arrivals, such as Europeans, within the endemic area of subtertian malaria, such as Bengali clerks in the Punjab, Egyptians in Sudan, etc. Thus it broke out among labourers employed on the Canal through the Isthmus of Corinth. Although blackwater was formerly very rare in W. Africa Negroes, it has become much more frequent amongst them since the institution of efficient antimalarial measures, so that their immunity to malaria has been lost, because they do not any longer contract malaria in childhood.

In its ætiology the subtertian parasite plays the chief rôle. Blackwater fever has been reproduced by S. P. James in paralytic subjects inoculated with *P. falciparum*, but no case has ever been observed in association with *P. vivax*, *P. malariae* or *P. ovale*, except as a hyperinfection.

Ætiology.—There now appears to be little doubt that quinine played a considerable part in the production of hæmolysis—the factor which “pulled the trigger” so to speak. Both quinine and the sulphonamides are lytic agents *in vitro* and it is known that in some normal, healthy persons quinine does occasionally cause hæmoglobinuria, resembling that of blackwater. There are also some extra susceptible malarial, but otherwise normal persons, in whom quinine, even in minimal doses, may produce a transient hæmoglobinuria. However, it must be distinctly understood that blackwater still occurs in native races to whom quinine is quite unknown. Indeed, on delving into history, we find that it was known to Hippocrates.

Little doubt can now be entertained upon the part quinine has played in blackwater, as shown by the work of G. M. Findlay (1949) amongst British troops in W. Africa during the second world war. The statistics for his conclusions may be briefly stated as follows:—The annual incidence of blackwater and the corresponding rates per 10,000 strength for each of five years were: 1941, 56.1; 1942, 82.9; 1943, 30.6; 1944, 2.3; 1945, nil. The peak incidence was from July to October, 1942. Of 179 cases, 132 were amongst persons in their first tour of duty in W. Africa and from 8–18 months residence. The earliest case occurred after only four weeks. Out of 152 only 14 stated that they had never suffered from

a clinical attack of malaria before the onset of hæmoglobinuria. In March, 1943, mepacrine (atebrin) was substituted for quinine as a suppressive. Thereafter there were only 19 cases of blackwater in Europeans and of these 14 still continued to take quinine: the final disappearance of blackwater coincided with that of malaria. On the other hand, blackwater fever cases in African soldiers in W. Africa increased in number year after year from 1941 to 1945.

The incidence of blackwater per 1,000 cases of malaria was in the course of five years: 0.86, 1.64, 3.56, 11.1 and 32.4. It is to be noted that African troops did not take any malaria suppressive drug, neither quinine nor mepacrine.

Sensitization.—Findlay and Markson (1947), in a series of experiments on African volunteers who had recovered from blackwater, produced relapses two, three and nine days after with an intramuscular injection of 5 ml. of subtertian malaria blood.

In order to develop one attack of blackwater fever it is necessary to be sensitized to the malaria parasite, and then it is possible to induce a second attack in those still sensitized by injection of a fresh dose of antigen, just as a new attack of asthma may be induced by exposure to the correct allergen.

Mechanism of hæmolysis.—Hæmolysis affects unparasitized, as well as parasitized, cells and this in a minor degree, is analogous to that observed in malaria, uncomplicated by hæmoglobinuria. Foy and Kondi postulate that the spleen may function as a reservoir for hypothetical hæmolysins. They have injected the hæmolysing blood of blackwater into a recipient who responded, not by reproducing blackwater or any other signs of hæmolysis, but by subsequently developing subtertian malaria.

Stephens and Christophers found in an attack of blackwater the red cells showed an increased resistance to different strengths of saline. But red cells from a case of blackwater are rapidly lysed, when transfused into a normal subject, and normal cells similarly so, if injected into a blackwater patient during a lytic phase, but it is apparent that lysis is not primarily due only to changes in the red cells of the patient. An important bearing in this connection is the discovery by Maegraith, Findlay and Martin (1943) of a heat-labile lytic agent in human tissues which is inhibited by normal sera. The latter factor is reduced during the hæmolytic crisis of blackwater. It is therefore suggested that in increased hæmolysis some acquired factor, possibly allergy to plasmodial protein, has disturbed the balance of the lytic agent and inhibitor to the lytic side. Maegraith and Devakul (1958) have shown the presence of lytic bodies in the plasma of some monkeys hyperinfected with *Pl. knowlesi* and it is in these particular animals that hæmoglobinuria occurs.

Liberated hæmoglobin-hæmoglobinuria can readily be demonstrated when the blood-serum is examined directly the crisis takes place and probably, by the time the pigment appears in the urine, a large proportion of erythrocytes has already been destroyed. The pigment is removed by phagocytosis by the reticulo-endothelium and converted into bilirubin, which in turn is absorbed by the liver cells and eventually appears in the bile; therefore some degree of hyperbilirubinæmia is common in blackwater. Some excess of hæmoglobin pigment is passed in the urine as oxyhæmoglobin (red in alkaline urine) or as methæmoglobin (dark reddish-brown in acid urine), but some remains in the plasma in the form of oxy- and methæmoglobin.

Some of the hæmoglobin, converted into methæmoglobin, is then excreted in the kidney and forms the cylindrical plugs in the tubules which represent the highly albuminous hæmoglobin-containing exudate which were formerly considered to constitute the mechanical cause of anuria.

Methæmalbumin (pseudomethæmoglobin) or *hæmatinalbumin* (Keilin), a pigment described by Fairley and Bromfield, is brownish in colour resembling

methæmoglobin by spectroscopic analysis; it is not reduced by Stokes's reagent or by ammonium sulphide. The molecule is too large to pass through the glomerular filter and so it does not appear in the urine. It is probably produced by union of hæmatin (ferric) in plasma with serum albumin. The pigment can be synthesized *in vitro* by the addition of alkaline hæmatin (ferric), prepared from pure hæmin, to human or simian plasma at 37° C. It therefore appears to be a chemical compound, consisting of a prosthetic group, oxidized hæmatin and a protein-natural serum albumin (crystal-albumin).

Yorke, Murgatroyd and Owen demonstrated that blood urea commonly rises in uncomplicated cases to 65 mgm. per cent. on the fourth day of the disease and there is a similar rise in severe subtertian malaria. In one of the Editor's cases 207 mgm. was recorded with ultimate recovery and even higher figures have been given by others. Other features are decrease in the plasma bicarbonate and a definite lowering of the alkali reserve in association with urea retention.

The mechanism of anuria has been the subject of some controversy and some of the older hypotheses have been called in question.

Maegraith and Findlay (1945) stated definitely that blockage of the renal tubules with debris and hæmoglobin products is not the deciding factor in the production of oliguria. The changes in the renal epithelium were thought to be partly due to anoxia.

Finally, Maegraith and Havard (1946), on the analogy of anoxia in other different conditions, such as surgical shock, cholera, crush injury, think that, in oliguria and anuria (tubulo-vascular syndrome), kidney changes are produced by lack of oxygen, resulting from changes in the renal blood flow.

There is a reduction in total blood flow through the kidney, a redistribution of blood flow through its component parts, and, in consequence, the cortex suffers from anæmia and anoxia, either relative or absolute.

Anuria results then from the renal anoxia syndrome and primarily from the failure of glomerular flow. On the other hand, Dawson and Findlay (1947), in experiments on the relation of hæmoglobinuria and anoxia with reference to blackwater fever in dogs and monkeys, have brought forward evidence to suggest that retention of histidine may be related to renal failure and development of pressor activity in the blood, whilst in patients with hæmoglobinuria they have demonstrated an increased excretion of histidine in the urine. It is suggested that in all cases of renal anoxia a proteolytic enzyme is liberated from the tissues and that it acts on various substances to produce polypeptides, which act as constrictors of the glomerular arteries and thus decrease the blood supply to the glomerulus.

Dacie, Israëls and Wilkinson have drawn attention to paroxysmal hæmoglobinuria of the Marchiafava type, the chief characteristics of which consist of chronic hæmolytic anæmia, associated with jaundice, and persistent hæmoglobinæmia. Autohæmolysis was demonstrated *in vitro* and shown to be dependent on the pH of the system. It has been shown that it is a nocturnal hæmoglobinuria, and that the urine is clear by day. The pigment is found to be methæmoglobin.

Favism in Greece and Sardinia is a syndrome which may be confused with blackwater fever, but is associated with a genetically determined deficiency of glutathione in the erythrocytes (Izeinberg *et al.*, 1955) (*see p. 21*).

Europeans are rarely attacked within the first year of residence in a blackwater-fever country, though cases have been reported after so short a residence as three or four months, and exceptional attacks may develop in those who have not previously shown definite symptoms of malaria. Comparable is the dramatic occurrence of blackwater fever in apparently healthy persons who have arrived in England, it may be as long as six

months, after the expiration of their duty, or on leave. As often as not, the patient gives no previous history of fever while in residence in the tropics. The explanation seems to be that a subtertian infection is lying latent until aroused by exposure to cold, alcohol, or some other factor.

The disease observes a roughly seasonal incidence; it is specially frequent in late summer and autumn in the southern states of America. On the West Coast of Africa it seems to be most prevalent at the close of the rainy season, or in August and September; in Central Africa and Nyasaland, especially in the highlands, a maximal incidence is seen during the wettest months, May to August, when the lowest temperatures are registered. In Southern Rhodesia, where the hot rainy season and the dry cold season are sharply defined, the malarial incidence increases after the rains in April; that of blackwater fever immediately rises also, and is maintained from March to July. During the 1914-18 war, in Salonika and Palestine, cases occurred among the troops especially during the cold winter months.

Pathology of Blackwater Fever.—The morbid anatomy and microscopic pathology of blackwater represent an hypertrophied picture of subtertian malaria.

Symptoms.—Some clinicians recognize a clinical condition which, for want of a better term, may be described as a *pre-blackwater state*, indicating a suspicion that blackwater is imminent, and it is wise to be on the look-out for the following clinical signs: The patient is one who has passed through several slight attacks of fever, or at any rate has been infected with the subtertian parasite for several months. The complexion is sallow, the conjunctiva icteric; the liver enlarged, congested and tender; the tongue furred; the spleen is generally enlarged, and constipation is the rule. There is usually persistent headache. The urine is dark, owing to the excretion of increased amounts of urobilinogen, and contains a slight amount of albumin. On examining the blood, scanty ring-forms of the parasite may be found, but it is noteworthy that cases of subtertian malaria with high fever and large numbers of parasites in the peripheral blood do not, as a rule, develop blackwater.

The *onset* of blackwater fever is usually sudden. A slight or, more generally, a very severe rigor is followed by intermitting, remitting, or irregular fever with marked bilious symptoms. The pyrexia and rigors do not seem to be the effects of the malaria parasites as much as of a sudden liberation of the products of hæmolysis; in other words, resembling a hæmoclastic crisis or "protein shock." Earlier or later in the attack, usually during rigor, the patient becomes conscious of aching pain—perhaps severe—in the loins, in the region of the liver and spleen, which are enlarged and palpable, and over the bladder. In exceptional instances these local pains are absent. In response to a somewhat urgent desire he passes water, when he is astonished to see that his urine has become very dark in colour, perhaps malaga-coloured, or possibly almost black. The fever continues, though it is not necessarily very high. Very likely he suffers from epigastric pain and distress, bilious vomiting to an unusual extent and, it may be, bilious diarrhœa; or he may be constipated. The pain in the loins and the liver-ache continue, and the urine becomes darker

and darker. By and by he breaks into a profuse sweat, which gradually subsides. The urine, which hitherto has been scanty, now flows freely; and after passing through the filter from dark brown to sherry red, becomes noticeably paler. Coincidentally with the appearance of the dark colour in the urine, before this, the skin and scleræ rapidly acquire a yellowish tint. This icteric condition persists, and even deepens, as the fever continues. When the fever subsides the patient is conscious of a feeling of weakness from which he recovers but slowly. Fever, with its accompaniments, may recur next day, or for several days; or it may cease to be remittent, or almost continued, in type. The hæmoglobinuria may recur with each rise of temperature, or there may be only one or two outbursts; it may continue for an hour or two only; or it may persist off and on for several days or even weeks.

In the more severe form of blackwater there is usually a very great amount of bilious vomiting, of intense epigastric distress, and of severe liver- and loin-ache. The urine may continue copious and very dark; or, continuing hæmoglobinous, it may gradually get more and more scanty, acquiring a gummy consistency, a few drops only being passed at a time. It is considered that the kidneys may excrete up to 36 per cent. of the total hæmoglobin in the blood, though this by no means represents the total amount liberated in many cases. Finally, urinary excretion may be completely suppressed.

In severe cases death is the rule. It appears to be brought about in one of three or four ways. The fever may assume the typho-adynamic type; or sudden cerebral, hyperpyrexial, or algid symptoms may supervene. Hiccup is a fatal sign. In other cases the symptoms may be like those consequent on sudden and profuse hæmorrhage—jactitation, sweating, sighing, syncope. Death may take place from sudden heart-failure after slight exertion, or from exhaustion consequent upon cyclical vomiting, or from sudden hæmorrhage from stomach or bowel. Or it may be that suppression of urine, persisting for several days, terminates, as cases of suppression usually do, in sudden syncope, or convulsions and coma. In very acute cases death may be due to focal necrosis of the liver. More rarely, nephritis may ensue and the patient die from uræmia three or four weeks after all signs of hæmoglobinuria and fever have disappeared, or he may succumb to some superimposed infection, streptococcal, septicæmic, or pneumonic. One attack of blackwater appears to predispose the individual to a second, and second attacks, or more than two, have been noted in Nigeria in about 20 per cent. of cases; according to Stephens, sixteen is the largest number recorded. It is necessary to lay special stress on these points, for when a man has suffered and recovered from two attacks, the third is generally fatal.

Blackwater fever is highly dangerous to pregnant women, during parturition or during the puerperium. Particular care should always be taken to guard them from malaria in these circumstances, especially in districts in which the subtertian parasite is most prevalent. Their blood

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should be treated with *P. vivax*,
of paludrine, doses of
5 gr. fever
fever

Should be frequently examined and they should take prophylactic courses of paludrine or atebirin from time to time.

Sequels.—Anæmia and debility are the common sequels of a blackwater-fever attack, but usually, under hygienic conditions, the recovery is astoundingly rapid. A curious sequel is cholelithiasis, owing to the formation of pigmented biliary calculi from inspissation of bile in the gall-bladder. K. D. Fairley originally drew attention to this phenomenon in a case in Australia, and the Editor has since seen two in which this was noted three weeks after the cessation of blackwater, and pigmented calculi were demonstrated at operation.

The urine.—If the characteristic dark-brown, generally acid, urine of a hæmoglobinuric case be stood for some time in a urine glass, it will separate into two well-marked layers; an upper of a clear, though of very dark, port-wine tint, and a lower—perhaps amounting to one-half or one-third of the entire bulk—of a somewhat brownish-grey sediment in which an enormous number of hyaline and hæmoglobin tube-casts are found, together with a large quantity of brownish granular material. Epithelium is also found. Blood-corpuscles may be entirely absent, or few. With the hæmoglobin there is also an escape of the serum albumin of the blood, for the urine, in many cases, turns almost solid on boiling. The precipitated albumin carries down with it, as it subsides, the dissolved and suspended hæmoglobin, leaving a pale-yellow supernatant urine. For some days after the urine has regained a normal appearance it will still contain albumin, though in gradually diminishing amount. Spectroscopic examination gives the characteristic bands of oxyhæmoglobin, as well as those of methæmoglobin. The appearance of oxyhæmoglobin is usual in very severe or fatal cases, methæmoglobin in the less severe or mild, in which the prognosis is more favourable. After the disappearance of the blood-pigments, urobilinogen may be demonstrated in pathological amounts and sometimes bilirubin.

Eye complications.—Hæmorrhages into the retina sometimes occur during the course of blackwater, and the Editor has seen one case of altitudinal hemianopia where there was total blindness in the lower half of the visual field.

Diagnosis.—The history of the patient, the attendant rigor, the hæmolytic icterus and hæmoglobinuria usually suffice.

Differential diagnosis has to be made from paroxysmal hæmoglobinuria, bilious remittent subtertian malaria, snake-poisoning, favism, yellow fever and leptospirosis; also from acute hæmolysis due to sulphonamides and pamaquine. If it be borne in mind that rigor, hæmoglobinuria, icterus and pyrexia are all in evidence at the outset in blackwater, and that it is acquired only in certain hyperendemic malarious centres, an error in diagnosis is impossible.

Treatment.—Patients who are suffering from or are threatened with hæmoglobinuria, who are in the *pre-blackwater state* (p. 60), or who have had this disease before should, on the slightest indication of fever, go to bed at once, keep the skin warm and scrupulously protected from draughts, and take plenty of warm fluid. If parasites are present in the blood

(usually *P. falciparum*, though there may be superinfection with *P. vivax*, *P. malariae* or *P. ovale*), the patient should be treated with full doses of paludrine or chloroquine. Patients threatened with blackwater fever should not travel; should it become imperative for any reason to move them, an injection of morphia should be given, or they may be kept under slight chloroform anæsthesia during the worst part of the journey. Injections of sodium luminal (*phenobarbitonum* solubile B.P., 10 gr., and a further 5 gr. two hours later) are said to keep patients quiet for two days. Glucose, in large quantities by mouth and intravenously in 5 per cent. solution, is indicated, as it has been shown by Kubo and Kondo that it may prevent hæmolysis of red corpuscles.

Specific treatment.—What promises to be an efficient, rapid and simple treatment is the administration of prednisone (Trowell and Vaizey, 1957). This is closely allied to cortisone and has the same anti-anaphylactoid effect without producing electrolytic imbalance; 10 mgm. roughly equal 50 mgm. of cortisone. Five consecutive cases of severe blackwater were given 10 mgm. three times daily for one day and then twice daily for six, reinforced, if necessary, with glucose and saline drip. The response was so prompt and satisfactory, so impressive, that it seems clear that the drug has a favourable effect on the hæmolytic process. This has been confirmed in two other cases by Pinhão (1957). Already in 1953 Linley Adams reported the favourable action of cortisone (150 mgm.) by injection.

Fluid.—Replacement of fluid and salt are necessary. Both may be lost by the patient by vomiting, diarrhoea or sweating. As far as possible fluid intake should be estimated and balanced against output, but it is a serious mistake to push fluids too vigorously. Should vomiting and coma prevent fluids being taken by the mouth, intravenous injections of physiological saline by the drip method are indicated. In coma or in convulsions drip transfusion with 5 per cent. glucose in saline should be given, but large quantities—eight or more pints—may be necessary. Marked restlessness should be controlled by injections of morphia.

In oliguria, or anuria, the fluid intake should be related to the output (urine, vomitus and fæces) plus 800–1,000 ml. for 24 hours. In sustained anuria, if facilities permit, calories may be supplied in the form of 40 per cent. glucose by drip through a plastic cannula passed into the superior vena cava, or by indwelling stomach tube. Aberrations in plasma electrolytes and concentrations must be watched for and corrected.

In threatened anuria hot fomentations may be applied to the loins and high rectal lavage with hot water appear to exert a diuretic effect. Physiological saline solution 6–8 ozs. at 100° F. should be injected into the rectum at intervals of half an hour.

Blood transfusions.—If the red cell count is one and a half millions or less, or the carriage of oxygen to the vital tissues is reduced, transfusions are absolutely necessary. These patients are very difficult to transfuse and the greatest care must be taken over cross-matching: transfusion reactions are very frequent. As citrated blood is liable to give severe reactions, injection of concentrated red cells is the best method, if facilities are available. It is most necessary, on account of autoagglutination, to perform *cross-matching* of the donor's corpuscles with the patient's serum

and *vice versa*. This is invariably routine: what is particularly important in view of the great anæmia is to cross-match donor's plasma with recipient's corpuscles. Repeated transfusions can be employed and as much as 500 ml. given on each occasion. There is no evidence that it arrests hæmolysis, but it is distinctly a life-saving measure. Wherever possible the drip transfusion method should be adopted. With replacement of active-functioning cells urinary excretion is often re-established and the blood urea falls to normal levels. As the excretion of ascorbic acid is increased in subtertian malaria and blackwater, this vitamin should be supplied in full doses during the convalescent stages. Potent proteolysed liver extracts by injection certainly help to restore hæmopoiesis and possibly folic acid (folvite) may also be useful.

It is advisable to give paludrine throughout the blackwater attack with the idea of preventing any possible relapse of malaria and to forestall any further hæmolysis.¹

Nursing is most important in the management of blackwater fever. If the stomach will retain food, this should be given in a bland and fluid form, but there should be no attempt at forcible feeding, especially with rich and indigestible viands. One precaution against syncope must be sedulously enforced: the patient must not be allowed to sit up, much less to get out of bed, until food has been retained and assimilated, and the risk of sudden death has passed. The foot of the bed should be raised on blocks.

If possible, the subject of blackwater fever should quit the endemic area, and never return to it or to any malarial locality; a severe attack, or a second attack, implying special susceptibility, should be regarded as a definite indication to leave the area. It should be remembered that blackwater patients are specially liable to retinal hæmorrhage and may also develop pigmented gallstones. In their enfeebled state they are also liable to secondary infections, such as pneumonia, streptococcal septicæmia and cardiac irregularities. A third attack is often fatal, though there are exceptional instances of seasoned individuals in West Africa who have survived more than ten.

Mortality of blackwater.—This varies greatly in the same and in different places, and under the same treatment. Some cases are so mild and transient, amounting, perhaps, to a single emission of hæmoglobinous urine, with little or no fever, that they are unattended with risk; on the other hand, a practitioner may encounter a run of severe cases which nearly all die. According to modern teaching the chances of survival depend upon the number of nephrons in the kidney which have escaped destruction as the result of renal anoxia. Formerly some old residents in Africa had passed through ten or more attacks with impunity. In Southern Nigeria and in Algeria the case-mortality has been as high as 50 per cent., but, as a general average, it may be put down as about 25 per cent.

Prophylaxis.—The prophylaxis of blackwater fever is obviously identical with that of malaria.

¹ *Phenamine (phenazone)*, p. 78, is liable to provoke blackwater in acute subtertian malaria and therefore should not be used.

In West Africa it has been concluded that mepacrine and now paludrine and daraprim have protected the Europeans against blackwater fever from 1944 onwards.

Other sequelæ of malaria.—The term *malarial cachexia* is applied to a group of conditions, more or less chronic, believed to be the result of an antecedent attack of severe malarial fever, or of a succession of such attacks, or of prolonged exposure to malarial influences.

The leading symptoms are those of anæmia, characterized by peculiar sallowness of the skin, yellow sclerotics, enlargement of the spleen and, it may be, of the liver.

In the young the general growth of the body is stunted, and puberty retarded. Abortion and sterility are common effects of malarial cachexia in adults.

Estimation of malarial prevalence.—The relative absence or prevalence of these enlarged spleens or “ague cakes” in the native population is a rough indication of the malarial risk in any particular district.

Another practical point is that these enlarged spleens are easily ruptured by a blow on the belly; this fact must be remembered in administering even mild corporal punishment to natives of malarious countries. Splenic ruptures are, of course, generally fatal, unless immediately operated on.

Six cases of ruptured spleen were operated upon in the East African campaign, in the second world war. After splenectomy, intravenous transfusion of blood from the peritoneal cavity is an easy and efficacious treatment. The blood is collected, strained through sterile gauze, citrated and given in the usual manner (Erasmus).

Splenic rate or index.—In estimating the amount of malaria in a community the splenic index has been found to be most reliable. Children between the ages of two and ten form the only safe guide (Stephens and Christophers), for among the inhabitants of a very malarious country the adults are more or less immune and their spleens are diminished in proportion. The infantile spleen rate *per cent.* is the basis of the endemic malariousness of a locality, though it is necessary to guard against a tendency to over-estimate its value. Barber, in the Philippines, working with children 5–10 years of age, obtained a splenic index of 13·8 and a parasite index of 11. This spleen-rate has come to be regarded as that of a community whilst the spleen-rate in adults is distinguished as the *adult spleen-rate*. The spleen-rate in adults may be in reverse relation to that of children.

It is difficult by any known method to detect changes in the spleen unless they are of some magnitude. Some authorities consider that a spleen must be twice its normal size before it can be felt. The degree of splenic enlargement may be measured with the child standing up or lying down. Considerable differences in the results obtained are given by the two methods, higher values being obtained in the recumbent position. In India and in the tropics generally, where gross degrees of enlargement are commonly encountered, the standing position is nearly always used. The best method is for the child to be drawn gently across the observer's knee, the hand being inserted beneath the scanty clothing and pressed against the costal margin while the child is told to take a deep breath. The degree of splenic enlargement is usually classified in finger-breadths below the costal margin. Obviously this method is liable to fallacies. The distance from

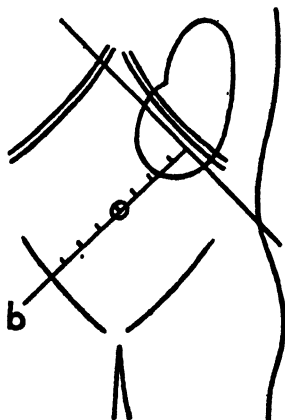


Fig. 8.—Schüffner's method of determining degree of splenic enlargement. (a) denotes the upper limit along the left costal margin; (b) a line drawn at right angles through the tip of the spleen and the umbilicus.

the costal arch to the pubes is very different in an infant of two years and a child of ten. Christophers devised a method by applying to the actual measurement (costal margin to apex of enlarged spleen) a correction based upon the nipple-umbilicus length of the child.

In the average Indian child of six years of age the four-finger spleen reaches to the level of the umbilicus. In malaria surveys, the following classification is generally adopted :

Spleen-rate greater than 50 per cent. = Hyperendemic.

Spleen-rate 25 per cent. to 50 per cent. = Highly endemic.

Spleen-rate 10 per cent. to 25 per cent. = Moderately endemic.

Spleen-rate less than 10 per cent. = Healthy.

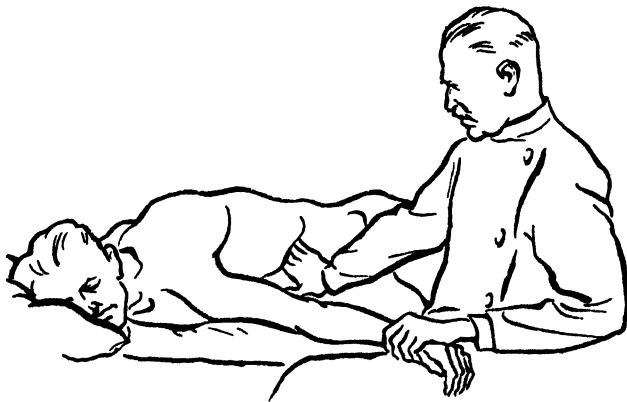


Fig. 9.—Method of spleen palpation. (After Schotter, Münch. Med. Wochenschr.)

The child spleen-rate gives the measure of endemicity, the average enlargement that of intensity.

Schüffner's method of estimating splenic enlargement has many advocates: a line is drawn along the left costal margin and a second at right angles to it passing through the apex of the spleen and the umbilicus (Fig. 8). The latter is divided into eight sections and the degree of splenic enlargement is assessed accordingly.

Occasionally an enlarged spleen has to be differentiated from an enlarged left kidney containing a cyst or a hypernephroma; this has usually a rounded lower pole and a smooth round margin. An area of resonance can be elicited on its anterior surface, caused by the resonant band of the descending colon. The urine contains albumin and casts. Considerable care is sometimes necessary in the accurate palpation of the spleen. This is best done by using the radial aspect of the right index finger with the patient recumbent on his right side and the abdomen relaxed, and the left arm extended (Fig. 9). Most authorities maintain that the greatest degree of splenomegaly occurs in *P. vivax* infections, but that in *P. falciparum* there is a higher proportion of smaller spleens.

Although the chronic fibrous spleen remains quiescent and does not interfere with general health, yet it may occasionally assume an active pathogenic role. Fairley has described a hæmolytic hypochromic anæmia associated with postmalarial splenomegaly of the Banti type in which splenectomy was followed by a hæmolytic megalocytic erythroblastic anæmia. The occurrence of hypersplenism secondary to chronic malarial splenomegaly is now generally acknowledged.

The *parasite-rate* or *index* is a simple percentage figure calculated from the number of persons actually showing parasites in the peripheral blood at the time of examination. Figures for children and adults should be kept separate, as the spleen-rate falls with age more rapidly than does the parasite-rate, which shows how many adults of a community are really "healthy carriers."

Many malarial infections are of a relatively high order—1,000 parasites per c.mm. or over—in one or two fields of a thick film, but a number of smaller infections remain undetected. It is clear, therefore, that to find one parasite one-thousandth of a c.mm. of blood must be examined, or approximately 5,000 red blood corpuscles. But to detect an infection of 100 parasites per c.mm. it would be necessary to examine 50,000 red blood corpuscles—or about 100 microscopical fields, each containing 500 r.b.c. The method of counting the parasites in 100 fields of a thin film is the simplest routine method when the results can be expressed as parasite rate per c.mm. Another simple method is to count the number of parasites for 100 or 200 leucocytes; assuming the latter number 6,000 per c.mm., the parasite density can be calculated. Although this index of Stephens and Christophers has been extensively employed it is found more convenient in practice to use the spleen-rate alone. *Macdonald's index* is the proportion of those children with enlarged spleens who show parasites on microscopic examination.

The parasite index can be obtained from the study of thick as well as thin films. Curves prepared from splenic and parasite *indices* according to age run parallel to a remarkable degree. The parasite index as a sign of infectivity is more reliable up to five years of age, after which to the age

of twenty-five it is on an average 10 per cent. less reliable than the splenic index.

Wilson and Clark, in a survey of 1,100 Haitian labourers and 2,007 school-children between 6 and 14 years of age, found that the parasite index, determined by the thick-film method, was of far greater value in estimating the prevalence of malaria than was the splenic index. Of 11,000 adults 23·5 per cent. had positive blood-films and 3·03 per cent. had palpable spleens: of 2,007 children, 50·52 per cent. had positive blood-films and 3·03 per cent. palpable spleens.

The *endemic index* includes all those who show either parasites or splenomegaly.

Liver and gall bladder.—Chronic hepatomegaly is a not infrequent sequel of malaria, and hepatic congestion may gradually become more or less permanent. *Siderosis* is produced from chemical changes in the liver undergone by *hæmosiderin*. Together with this there may be chronic engorgement of the gall-bladder, which predisposes to cholecystitis and cholelithiasis. It is small wonder that with such a polycholia pigmented calculi are apt to form. For instance Vauthey has recorded 23 cases of biliary colic during an attack, and 71 in which biliary attacks occurred subsequently.

IMMUNITY IN MALARIA

In the course of malarial infection a certain degree of tolerance may develop.

In heavily-infected endemic districts, malaria is specially likely to appear in small children, and of these a proportion die early, while others acquire a remarkable degree of immunity through repeated re-infections. It has often been remarked that dark-skinned children with enormous spleens and a rich stock of malaria parasites in their blood run about fever-free, and apparently robust, but they have usually at some time passed through a few years of miserable ill-health. As these children grow up, their immunity becomes stronger and, after twenty years of age, they may remain quite free from clinical signs, and even splenic enlargement may disappear.

It is generally accepted that malaria, like other protozoal diseases, differs from bacterial infections in that the causative parasites do not disappear, but remain in the body, where a balance is established between the resistance of the organisms and the inherent tendency of the parasites to increase. Sergeant, Parrot and Donatien have coined the term "*pre-munition*" to characterize the balance between immunity and re-infection. It is an active immunity consequent upon infection, but also contingent on the concomitant presence of plasmodia. This *equilibrium-tolerance* of the parasites by the host should be compared with allergic conditions of symptomless latency in tuberculosis and syphilis.

Taliaferro and his associates have assigned an important rôle to the reticulo-endothelium and a similar condition has been found by Cannon and Taliaferro in birds infected with avian plasmodia. Ziemann and others endeavoured to distinguish between immunity to the toxins and that due to the parasites. In the latter case the organisms disappear gradually from the body.

Taliaferro and Mulligan attribute a considerable rôle to the macrophage cells. The reticular cells of the spleen and bone marrow rapidly become converted into the phagocytic phase and may play an essential part in the local defence of these organs.

It is well known that the Negro in Africa, although he does get fever, does not get it so frequently or so severely as does the European, although the latter is less exposed to infection. Indeed, malaria in natives is so often asymptomatic as to give the impression of quite a different disease. Amongst the Malays Schiffner observed an immunity to malaria parasites, as described by Ziemann. Of the young children, 38 per cent. were parasite carriers, while in the older ones it was as high as 50 per cent. The parasite index in adults was 8-11 per cent., and of those examined, 92 per cent. showed enlargement of the spleen. Christophers (1924) found the same conditions in India. In most districts in the tropics all three classical forms of the malaria parasite occur, and therefore immunity may be produced against all three. In an untreated population, it is found that among children benign tertian parasites disappear most quickly, quartan parasites next and subtertian persist the longest. This is also the case among adults in whom the ring forms of the latter parasite predominate while crescents are very scanty. Thus natural immunity in native populations is the result of natural selection, but each species of malaria parasite appears to be composed of different immunological strains. Natives immune to strains of *P. falciparum* of their own districts may be subject to attacks of subtertian malaria after moving to other areas as a result of infections with new strains.

Sinton, who has given considerable attention to this aspect of immunity, believed that there are two methods of attack upon the malaria parasite and its toxins, viz. (a) cellular, and (b) humoral, and that these two factors are closely associated and act in combination.

That the immunity produced by previous infection with an homologous strain of *P. vivax* is complete has been shown recently by Shortt & Garnham in an experimentally produced human infection. It would seem that in such an immune individual the E.E. forms in the liver, which result from a fresh and overwhelming infection, are engulfed by invading leucocytes and destroyed to such an extent that no fever results.

The humoral factors are much less certain; in acquired immunity there is certainly development of specific antibodies and these are probably produced by the macrophage system as the result of stimulation of ingested parasites, acting as a specific antigen. The element concerned may be a lysin, or possibly an opsonin. Antitoxic substances are also probably produced, and there is some evidence to show that a certain degree of passive immunity can be transferred by the injection of serum from an immune subject. Macdonald has even asserted that the existence of group immunity makes control in some cases undesirable. In rats experimentally infected with *P. berghei* Bruce-Chwatt and Gibson have shown that a certain amount of immunity is transmitted to the young via the placenta and that, moreover, a passive transfer of protective antibodies could be effected through the serum of adult rats. Terry (1956), in confirming this work, has been able to convey immunity in serum given by the mouth.

In West African holoendemic areas the child population is highly pre-mune by five years of age.

Considerations such as these explain the sudden and severe outbreaks of malaria in endemic districts. Sometimes meteorological causes combine to render conditions more favourable for the development of the transmitting anophelids with consequent increase and spread of the disease, as in the Ceylon epidemic of 1934. Macdonald considers that in the first

MALARIA PARASITES. $\times 2,000$ **A.—SUBTERTIAN PARASITE (*Plasmodium falciparum*).**

- Fig. 1.—Subtertian rings. Note the marginal form and, in one, double chromatin dots.
- Fig. 2.—Quarter-grown parasite. When seen in the peripheral blood this denotes a severe infection, as it normally occurs in the capillaries of the internal organs. Note discolouration of cell, its irregularity and the pernicious stippling—known also as “Stephens’s” and “Christopher’s” dots, also as “Maurer’s spots” or clefts.
- Fig. 3.—Schizogonic stage, or rosette form, with thirty spores, also usually in capillaries of internal organs—seldom seen in peripheral blood.
- Fig. 4.—Male gametocyte (crescent).
- Fig. 5.—Female gametocyte (crescent) showing concentration of chromatin and pigment.

B.—BENIGN TERTIAN PARASITE (*Plasmodium vivax*).

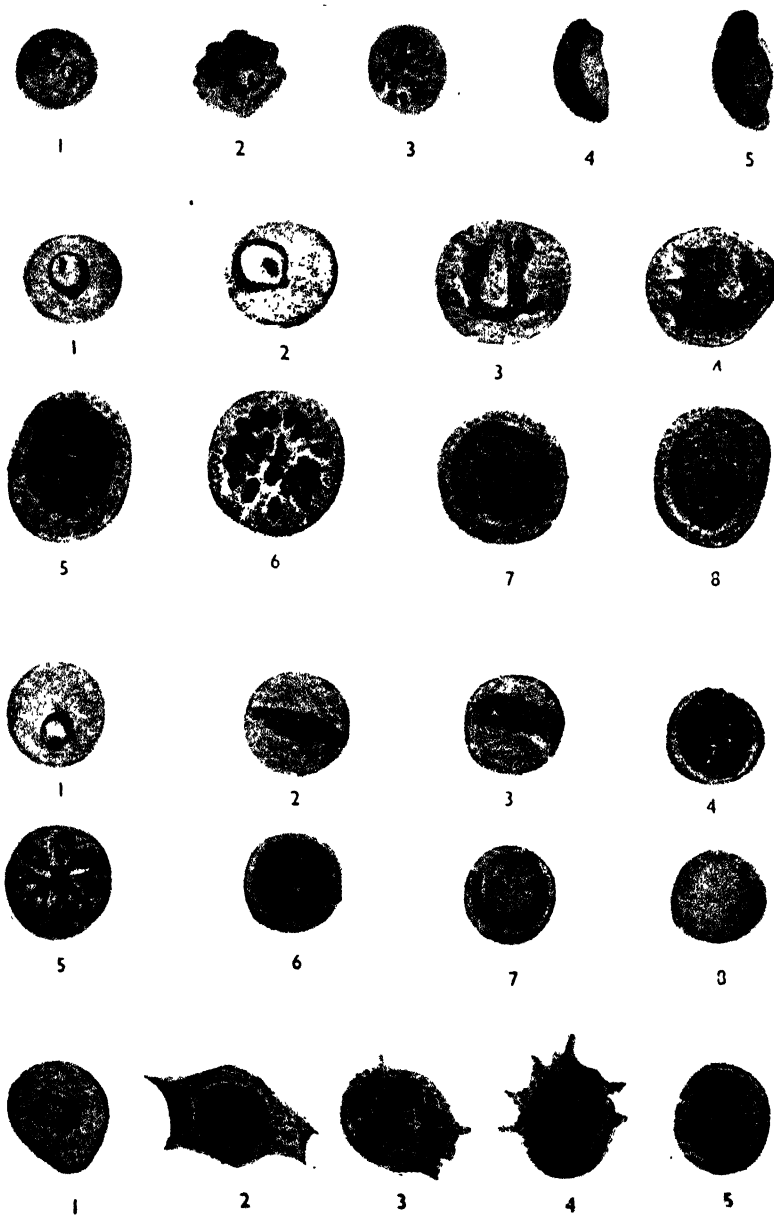
- Fig. 1.—Young ring form.
- Fig. 2.—Quarter-grown parasite. Note Schüffner’s dots and slight enlargement of corpuscle.
- Fig. 3.—Half-grown parasite. (Amœboid form).
- Fig. 4.—Three-quarter parasite. (Amœboid form).
- Fig. 5.—Presporulating stage showing fragmentation of chromatin.
- Fig. 6.—Complete schizogony. (Rosette stage with 20–24 spores).
- Fig. 7.—Male gametocyte. Note loose arrangement of chromatin and purple tinge of protoplasm. The pigment is coarser and blacker than in the female.
- Fig. 8.—Female gametocyte. Note compactness of chromatin and blue tinge of protoplasm.

C.—QUARTAN PARASITE (*Plasmodium malariae*).

- Fig. 1.—Ring form.
- Fig. 2.—Quarter-grown parasite (“band form”). Note corpuscle is not enlarged.
- Fig. 3.—Half-grown parasite (“band form”). Note the scattered dark pigment.
- Fig. 4.—Presporulating stage.
- Fig. 5.—Complete schizogony. (Rosette stage with 8 spores).
- Fig. 6.—Male gametocyte. Note purple tinge of protoplasm with heavy pigmentation, coarser and blacker than in the female.
- Fig. 7.—Female gametocyte. Note blue tinge of protoplasm. (Stipplings, when present in the blood corpuscle, are known as Ziemann’s dots.)
- Fig. 8.—Normal red blood-corpuscle for comparison of size.

D.—OVALE TERTIAN PARASITE (*Plasmodium ovale*). (After James, Nicol & Shute.

- Fig. 1.—Ring form. Note Schüffner’s dots.
- Fig. 2.—Presporulating stage. Note irregular and oval shape of corpuscle with coarse and prominent Schüffner’s dots.
- Fig. 3.—Complete schizogony. Note irregular distribution and oval shape of spores, and also distortion of corpuscle.
- Fig. 4.—Male gametocyte. Note coarse Schüffner’s dots and purple tinge of protoplasm.
- Fig. 5.—Female gametocyte. Note marginal arrangement of pigment.



MALARIA PARASITES

PLATE II

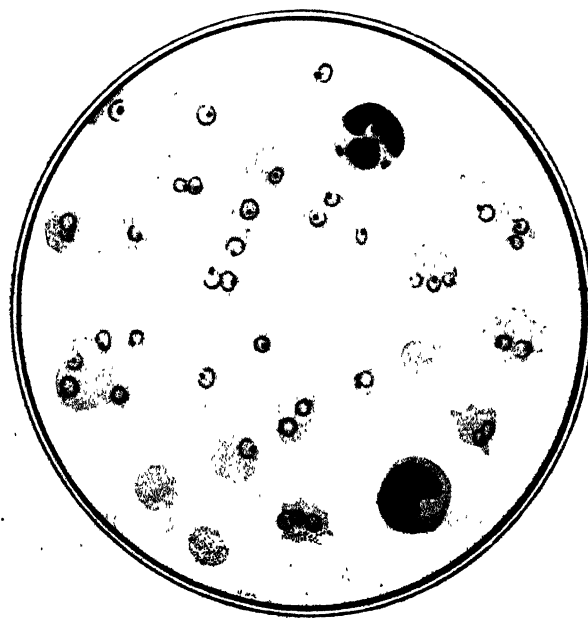


Fig. 1.—Blood-film from fatal case of subtertian malaria, showing heavy "ring" infection. (*Giemsa's stain*).

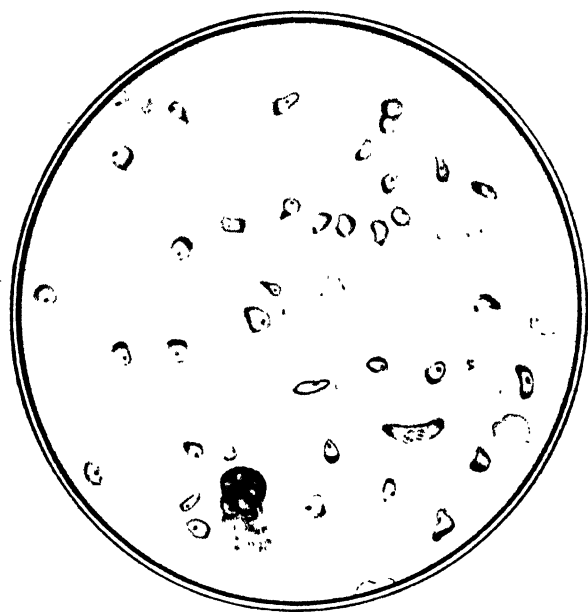


Fig. 2.—Thick blood-film preparation of subtertian rings and crescent stained by Leishman to show appearances after dehemoglobinization, $\times 1,000$ (From a preparation by Dr. H. Seilein.)

two years of life in hyperendemic areas, and perhaps for longer periods, in places of low endemicity, superinfection can be considered as a normal happening.

The maximum adjustment of the parasite to its host is attained when the former is able to survive without detriment to the latter. This state is what is known as fully developed premunition, the best example of which is found in *piroplasmosis* of cattle in U.S.A.

DIAGNOSIS OF THE FOUR CLINICAL VARIETIES OF MALARIA

The recognition of the various forms of malaria parasite in the peripheral blood entails a knowledge of blood examination. For the details of this and of the methods of staining blood the reader is referred to the Appendix, p. 1091. Most workers prefer the thick-drop method as offering a more certain chance of discovering the parasites when scanty in the peripheral blood, but it is by no means such a certain method of distinguishing the species, and requires considerable experience in order to do so.

Complement fixation.—This method of ensuring an accurate diagnosis in chronic cases was originally suggested by Gordon Thomson and considerable attention has been paid to it. As antigen an emulsion of an organ rich in parasites, as well as artificial cultures of plasmodia, have been employed.

Coggeshall (1941) described his special method with an antigen prepared from red cells infected with *Plasmodium knowlesi*, but it is of purely academic interest.

Wassermann reaction.—About 28 per cent. of malarial bloods in the acute stages of malaria, when parasites are plentiful in the peripheral blood, give a positive Wassermann reaction; but this is not so in either the chronic or quiescent stages. This fact has to be borne in mind in excluding syphilis in a malaria-infected subject.

Saunders and Turner (1935) believed that these results are not specific, but that malaria in the acute stage gives rise to anti-complementary reactions. The latest work by Kitchen, Webb and Kupper supports this view. They inoculated 30 persons with *P. vivax* and *P. falciparum* and tested the blood at intervals with the Wassermann and Kahn reactions. They obtained positive tests in every case in which malaria developed clinically; 72 per cent. of positive reactions appeared during the third and fourth weeks after inoculation of malaria, and these remained positive for more than three weeks in 60 per cent. The highest percentage of positives occurred from fifteen to twenty-one days after the last paroxysm.

Try tested 246 malaria patients, the blood being taken when the temperature was normal: 11·78 per cent. gave a positive Wassermann reaction. Of 97 with subtertian malaria, 8·2 per cent.; of 110 with benign tertian, 11·8 per cent.; of 39 with quartan malaria, 20·5 per cent. were positive. Potter (1945) found in the case of *P. vivax* that all serum reactions returned to normal within 30 days.

Diagnosis by sternal puncture.—Schretzenmayr (1939) claimed that sternal puncture is a simple procedure, and that it should be adopted as a routine diagnostic measure; he found parasites by this method in 19 cases although blood films were negative. Aitken, Rumball and others (1943) have used this method. They found it valuable in atypical cases, where routine examination of the peripheral blood was negative, especially in subtertian infections. A sternal puncture needle is unnecessary, and a stout truncated lumbar puncture

needle can be used. It is inserted vertically through the centre of the sternum at the level of the second intercostal space and pressed firmly through the cortex. Resistance decreases when the marrow is entered. Thick drop preparations can be made, and the fluid contains more parasites than the peripheral blood. Of 294 cases of obscure illness, 256 were diagnosed by blood films, the remaining 38 by sternal puncture. Many of the latter had previously been treated as sandfly fever or neurasthenia.

Diagnosis from clinical signs.—The most important clinical sign is periodicity of the fever, which occurs in its most typical form in the tertian and quartan infections; in the subtertian, however, fever may be most irregular, or there may be no pyrexia at all.

Enlargement of the spleen is a common clinical sign in all forms of malaria. In old-standing infections it may be very large indeed, and occupy the greater part of the abdominal cavity, but in early, and it may be very severe, cases it may not be sensibly enlarged at all, and therefore fails entirely as a clinical guide; usually, however, in the absence of splenic enlargement, splenic *pain* is present during the attack. Moreover, the patient may be suffering from some totally different disease, and the palpable spleen may be the result of a long-standing malaria infection, quite unconnected with the attack in question.

To the clinician accustomed to many cases, the general appearance of malaria patients, the bright glistening eye, set in rather a dusky orbit, contrasted with the pale and ochreous complexion, combine to create an almost diagnostic appearance. Amber coloured urine due to excessive urobilinuria, especially in subtertian malaria, and even in the absence of parasites in the peripheral blood, may be suggestive.

Diagnosis by the history.—Sudden fever in a previously healthy person who has recently arrived from a malarious country usually turns out to be malaria. The patient will generally give a history of similar attacks while resident abroad, but there are exceptions to this rule, for, occasionally, residents of tropical countries may develop their first attack of malaria shortly after arriving in a cold climate, and this attack, aggravated by the conditions, may run a very severe course; this is especially the case with recent arrivals from the West Coast of Africa, and it is true for both benign tertian and subtertian infections, the parasite lying dormant in the blood-stream, perhaps as long as eight months; in the benign form a year or more. It should be borne in mind that, in the case of *P. vivax*, *P. malarie* and *P. ovale* all "prophylactic" drugs are in reality only suppressive. A possible diagnosis of malaria should therefore not be discounted on the grounds that drugs were continued for the advised 14 days after return to a non-malarious country.

An actual description of the febrile attack itself may be suggestive. The rapid rise of temperature, the history of the cold, the hot, and the sweating stages, the rapid defervescence of the fever, and the subsequent sense of well-being, are more characteristic of a malarial attack than of any other febrile disease. At times periodicity is a trustworthy enough clinical test. *Tertian and quartan periodicity usually occur only in malarial disease, but have been seen in meningococcal septicæmia.*

DIFFERENTIAL DIAGNOSIS OF MALARIA

The differential diagnosis of malaria entails a knowledge of all fevers, both tropical and non-tropical.

The following are often mistaken for malarial fever: cerebro-spinal meningitis; fever of urinary origin (sometimes renal calculus); the fever attending the passage of gall-stones, or inflammation of the gall-bladder; that associated with pyelitis and surgical kidney; perineal abscess, amœbic hepatitis and amœbic abscess of liver; lymphangitis, particularly that form associated with elephantiasis and other filarial diseases; undulant fever, relapsing fever; trypanosomiasis; kala-azar; "short-term fevers" of which dengue and sandfly fever are the most typical; the fever associated with tuberculous disease, with ulcerative endocarditis, with some types of pernicious anæmia, with splenic leucocythæmia, with visceral syphilis, with pulmonary carcinoma, with rapidly growing sarcoma, with forms of hysteria, and with many obscure and ill-defined conditions.

Primary atypical pneumonia in its initial stages may resemble a malarial attack, and its recognition gave rise to difficulties in the Middle East campaign. Campbell (1943) described two clinical groups. The first consisted of patients who had both malaria and pneumonia, the second of those admitted with malaria who later developed pneumonia. The routine use of X-rays is indispensable; it reveals the typical mottling of the lung bases.

Priest, Kilham, Javett and Sachs found that meningococcal septicæmia may produce tertian, or even quartan, periodicity somewhat resembling that of the corresponding forms of malaria.

Differential diagnosis of special forms of subtertian malaria.—There is a natural tendency for medical men, unacquainted with the clinical forms of subtertian malaria, to diagnose its various symptoms as manifestations of some other disease. Even surgical conditions, such, for example, as appendicitis, intestinal obstruction, or other acute abdominal disorders calling for urgent operative interference, may be suspected. The following statement is based upon actual diagnoses which have been made on clinical grounds alone, without the confirmation of a microscopic examination, but which subsequently proved to be cases of subtertian malaria:

- (a) *Cerebral forms* of subtertian malaria are apt to be mistaken for heatstroke, mental derangement, hysteria, alcoholism, aphasia, convulsions, epilepsy, cerebro-spinal meningitis, or plague.
- (b) *Abdominal forms* for dysentery, both amœbic and bacillary, cholera, intestinal obstruction, appendicitis, biliary colic, cholecystitis, hæmorrhagic pancreatitis, or liver abscess. Malarial appendicitis can be distinguished on clinical grounds by overcoming the muscular defence by patient palpation, from the subsequent passage of fæces and flatus, the dicrotic, full pulse, flushed facies, and the rapid fall in temperature after a profuse sweat.
- (c) Those with *cutaneous petechias* for measles, endocarditis, or purpura.
- (d) *Febrile cases* with remittent pyrexia for influenza, rheumatic fever, enteric, phlebotomus fever, trench fever, paratyphoid, or relapsing fever.
- (e) *Icteric cases* for yellow fever, Weil's disease (leptospirosis) or infective hepatitis.
- (f) *Cachectic cases* for acute nephritis, pernicious anæmia, spleno-medullary leucocythæmia, debility, or pulmonary tuberculosis.
- (g) *Edematous forms*, exceptional cases with general anasarca, ascites and polyuria, may be mistaken for beriberi.

TREATMENT OF MALARIA

(BENIGN TERTIAN, QUARTAN, OVALE TERTIAN AND SUBTERTIAN)

General management of a case of malaria.—Every case of malaria with fever should be nursed in bed and treated seriously, for severe symptoms may develop at any moment; he should remain confined to bed till he has been afebrile for 48 hours. The room should be darkened to mitigate the photophobia; a sports shade or eyeshade serves this purpose very well.

Special attention should be paid to clothing; the patient's feet must be kept warm with bed-socks, and after the stage of perspiration the bedclothes should be changed. Attention to the food is also necessary. During the acute stages it is best to give plenty of water and lemonade to drink, while the food itself should be fluid and easily digestible. During the convalescent stages, if the patient has an appetite, full diet should be substituted, and there is no point in denying to patients who are used to it a strictly moderate amount of alcohol; beer and stout in moderation are useful.

Antimalarial drugs fall into 6 groups—

- (1) Cinchona alkaloids, including quinine.
- (2) 4-aminoquinolines, including chloroquine, sontochin, camoquine.
- (3) 8-aminoquinolines, including pamaquin, pentaquine and primaquine.
- (4) Diguanydes, which includes proguanil.
- (5) Acridines, which includes mepacrine (or atebrian).
- (6) Pyrimidines—daraprim (pyrimethamine).

The degree of immunity to malaria necessarily plays a great part in treatment. Obviously the effect of antimalarial drugs and the length of treatment have to be adapted to immune, partially immune and highly susceptible subjects.

I. QUININE

Quinine is an alkaloid isolated from the bark of the cinchona tree, originally a native of South America, but now cultivated in Eastern countries, especially Java, where the most prolific variety, *C. ledgeriana*, has been produced. Recently this drug has been successfully synthesized by Woodward and Doering in America. There are many salts of quinine, though at present most are merely of historic interest.

*Quinine hydrochloride*¹ is fairly soluble and is the form most usually dispensed. The *sulphate* is cheaper, though almost insoluble in water. *Sugar-coated pills* are effective and are easy to swallow. To dissolve the sulphate 10 minims of acid. sulph. dil., or acid. phosph. dil., should be added to every 10 gr. of quinine sulphate.

Other forms of quinine.—*Euquinine*, or the ethyl carbonate, and *quinine tannate* have the advantage of being tasteless as they are practically insoluble and are specially suitable for children. *Quinine alkaloid*, though almost insoluble, appears to be absorbed from the intestinal tract.

Five different alkaloids are known from the cinchona bark, but of these

¹ Quinine hydrochloride has a pH of 6.5; the dihydrochloride 3.5. Contrary to what is usually stated the former is suitable for parenteral injection and is indeed less painful than the dihydrochloride.

quinidine and *cinchonine* alone have any action on malaria, especially benign tertian and quartan.

Dosage of quinine.—The maximum dose for the adult European is about 30 gr. (2 grm.) daily. Larger ones than these are toxic and, as frequently proved, not more efficacious.

For children the dose is one-twentieth of that of the adult for each year of age. A child of five should receive one-quarter of the adult dosage, whilst to those above fifteen the adult dosage may be given.

Excretion of quinine.—It has been shown that quinine is excreted in the same manner by whichever route it is administered. It appears in the urine within 15 minutes and one-quarter of the total is excreted by this route, and the highest concentration is 7–11 gr. quinine base per litre. Large amounts are excreted in the faeces. This holds good only for the tannate or carbonate, not for hydrochloride, hydrobromide, bisulphate, sulphate or even for the insoluble ethyl carbonate.

The *Tanret*¹ reaction in the urine has given important indications in the treatment of subtertian malaria (Howie and Murray-Lyon, 1943), especially regarding *absorption* of quinine. The majority give positive reactions between one and five hours after the exhibition of quinine. In some the reaction may remain negative until intravenous quinine has been given. A most practical method of ascertaining whether quinine is being absorbed consists of coating quinine pills with methylene blue, which discolours the urine green.

Quinine, in prophylactic doses, is excreted in the milk of nursing mothers.

In naturally acquired malaria, especially benign tertian, continuous and prolonged quinine therapy may be of little benefit in preventing relapses though therapeutic or malaria induced by blood-inoculation appears to be extraordinarily amenable.

Toxic effects of quinine.—The milder manifestations are nausea, tinnitus, dizziness, tremors and palpitations. Vomiting is occasional and may be controlled by 10–20 min. of 1:1,000 adrenalin injected with $\frac{1}{2}$ oz. of water.

Idiosyncrasies are exceptional—some become hypersensitive from long-continued dosage. In others it produces urticaria: in others again, cutaneous eruptions varying from a mild erythema to weeping eczema, or an exfoliative dermatitis.

Contrary to popular belief there is no evidence that permanent deafness may be brought about by quinine.

Quinine amaurosis, or *amblyopia*, generally results from gross overdosage (80–160 gr.), but exceptionally in those with pronounced idiosyncrasy, temporary blindness may follow even moderate doses. According to McGregor (1944) this is due to damage to the retinal cells with the production of a "sieve-like" field. The milky appearance is attributed to ischæmia and the cherry-red spot in the macula to blockage of the central artery.

INJECTIONS OF QUININE

(a) Intramuscular injection

This method has been much criticized. The general consensus of opinion is that it is a valuable therapeutic measure under certain circumstances.

¹ The *Mayer-Tanret* reaction consists of two solutions:—A, Mercuric chloride 1·35 grm. aq. dest. 75 ml.; B, Potass. iod 5·0 grm. aq. dest. 30 ml. The two solutions are mixed in 100 ml. aq. dest., plus 10 ml. urine to each of two tubes. If they remain clear, quinine is not present, if turbid it is. Albumin is removed by a drop of acetic acid.

Its dangers have been much exaggerated and probably were due to abuse.

The indications are non-absorption of oral quinine owing to severe vomiting, the presence of several toxic symptoms or of large numbers of parasites in the peripheral blood. The most suitable salts for this purpose are the hydrochloride, or the dihydrochloride which is soluble in its own weight of water. Pain is caused by the acidity of the solution; that of the latter is pH 8.5, of the former 6.1. For that reason the hydrochloride salt is to be preferred. The hydrochloride is best when combined with urethane.

Quinine hydrochlor.	. gr. x
Urethani gr. v
Aq. dest. . . .	ad 2 ml.
Sol steril . . .	(pH = 6.1)

Site.—The usual site for injection is the gluteus maximus muscle at a point on a horizontal line through the apex of the great trochanter (Fig. 10). This point lies well above the exit of the deep-lying great sciatic nerve, which may be injured by plunging the needle below the fold of the buttock so that paralysis of the leg may result. Pain is minimized and absorption aided by massaging the site of injection for some three minutes. A stout, preferably platinum-iridium, needle is driven home rapidly deep into the muscle after cleansing the skin thoroughly. Should the salts of

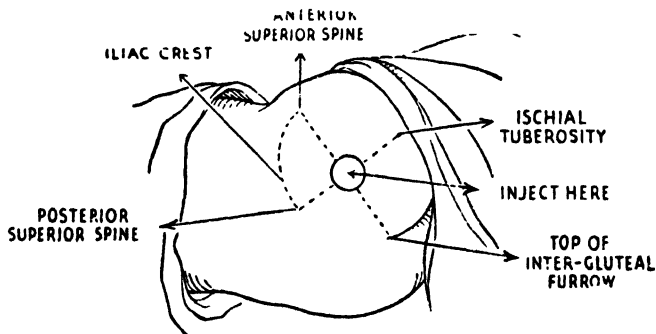


Fig. 10.—Diagram showing the site for a quinine injection.
(Burroughs, Wellcome & Co.)

quinine be used in tabloid state, their solution must be freshly prepared and boiled and the syringe and needle thoroughly sterilized. In children, especially, the injection should be given slowly and in dilute solution. It has been shown that concentrated solutions of quinine are rapidly absorbed from the tissues and that its action upon the parasites in the blood is rapid.

Localized necrosis of the muscular fibres is apt to occur after quinine injection.

(b) *Intravenous quinine injections.*—In the pernicious or acute forms of subtertian malaria, especially when there is cerebral involvement, where it is important to obtain rapid and powerful action, quinine should be injected intravenously. The hydrochloride or dihydrochloride salt should

be employed in doses of 10 gr. dissolved in 10 ml. of distilled water. In algid cases or those with cardio-vascular collapse it is advisable to reinforce with glucose, 5 per cent. in saline in amounts of $\frac{1}{2}$ to 1 pint. The solution of quinine should be boiled in a test tube, drawn up into a sterile syringe and injected into the median basilic vein. On introduction the plunger of the syringe should be withdrawn slightly to permit blood to enter the barrel. The injection should be made slowly and at least three minutes spent over the operation. One dose of 10 gr. usually suffices to stop the fever and to cause disappearance of most of the parasites within eighteen hours.

The use of quinine as a prophylactic is now obsolete. As a therapeutic weapon it only retains a place in the pernicious or hyperacute types of *P. falciparum* infections when, preferably, it should be given intravenously.

II. 4-AMINOQUINOLINES

Chloroquine, Resochin (German) (for synonyms, see p. 869). This drug concentrates in the liver and is a schizonticide in all forms of malaria. The salt usually employed is the diphosphate. Tablets of 0.25 grm. contain 0.155 grm. of the base. The maximum initial dose is 1.0 grm., followed after 6 hours by 0.5 grm., then 0.5 grm. on second and third days. The duration of the fever is cut short with this drug, usually lasting about 80 hours. Others have reported equally good effects with smaller doses, such as 0.5 grm. followed by 0.25 grm. after 6-8 hours, and then a single dose of 0.25 grm. on each of three successive days. It also exerts a suppressive effect when given once weekly in doses of 0.5 grm. By intramuscular injection chloroquine can be given a dose of 200 mgm. of the base¹ repeated in four hours, but oral treatment should be started as soon as is possible. In the form of the dihydrochloride it has been injected intravenously in doses of 5.7-14.9 mgm. of base per kg. body weight. A reasonable dose is 5 ml. of a 5 per cent. solution. Mohr has given double this amount to all forms of malaria by injection with excellent results. Jelliffe (1953) has shown in Nigerian (i.e. partially premune) children of 4-27 months that one intramuscular injection of 5 mgm. base per kg. was a radical cure.

Side-effects.—In very large doses chloroquine may produce difficulties in vision, bleaching of the hair, when given for a year, especially in blondes, slight weight loss and headaches. Occasionally vomiting and gastric disturbances have been reported.

Harris (1957) has drawn attention to deaths in children, especially, who received more than the standard dose of 5 mgm./kg. by intramuscular injections.

Camoquine (see p. 868) is given as the bihydrochloride in tablets of 0.2 grm. by mouth. The single dose is 0.6-1 grm. for adults and for children it is given on the basis of 10 mgm. per kg. body weight. Thus those of five to fifteen receive 0.2 grm. and over that age 0.4 grm. As a suppressive it is said to be more effective than chloroquine in doses of 0.6 grm. weekly.

¹ 0.6 grm. of base equals 1 grm. chloroquine diphosphate.

III. 8-AMINOQUINOLINES

Pamaquin (plasmoquine (see p. 876)). On account of its toxicity the doses are small. In doses of 0.04 grm. daily it acts as a schizonticide in *P. vivax* and *P. malariae* malaria, but is less effective in *P. falciparum*. It is a powerful gametocide in all malaria infections. Gametocytes are destroyed before the schizonts and crescents of *P. falciparum* disappear after five days' dosage. In combination with quinine it was formerly much used in treatment of *P. vivax* malaria in which it is a suppressant. At present there are only two indications for its use: (a) to clear the blood of gametocytes and thus limit the infection of a mosquito population (of minor importance); (b) to eradicate the EE forms of *P. vivax*, *P. ovale* and *P. malariae* from the liver and thus to prevent relapses. Of toxic effects the commonest is cyanosis (drug methæmoglobinæmia), abdominal pains, vomiting; and most severe of all, methæmoglobinuria (especially in *P. falciparum*). This is due to intravascular hæmolysis and resembles blackwater fever also in its pathological effects. Toxic hepatic necrosis and hæmorrhagic nephritis may also ensue, and there is some evidence that it may provoke blackwater fever. Parenteral injections are dangerous.

Pentaquine in the form of yellow needles is slowly soluble. In prolonged treatment of 60 mgm. with 20 gr. quinine it enhances the action of the latter and eradicates *P. vivax*. It is said to be toxic for Negroes and children. A compound of quinine sulphate with pentaquine phosphate has now been prepared under the name of *Quiniplex* for the treatment of *P. vivax* malaria (p. 878).

Primaquine, in the form of diphosphate, is a compound closely allied to pentaquine and has been used together with quinine sulphate in reducing the relapse rate of the Chesson strain of *P. vivax* malaria (Edgecomb and colleagues, 1950). It appears to be superior to pamaquin and isopentaquine. In doses of 15 mgm. of the base daily for 14 days it has been found to give rise to methæmoglobinuria, especially in Negroes in U.S.A. The hæmolytic effect can be demonstrated *in vitro* (Beutler, Dern and Alving). Primaquine exerts its most powerful effect in the early tissue stages of *P. falciparum* and *P. vivax*. It can therefore be used as a causal prophylactic (Arnold, Alving and others, 1955). The most valuable property of primaquine is its efficiency—like that of pamaquine in eradicating EE forms from the liver to secure radical cure of *P. vivax*, *P. malariae* and *P. ovale* infections.

Like pamaquine, primaquine is apt to produce drug-induced hæmolysis, especially in Negroes, Indians and other coloured races and this has now been shown by Dern (1954) to be due to an intrinsic abnormality of the red cell and the presence of Heinz bodies.

IV. DIGUANIDES (PROGUANIL OR PALUDRINE)

Proguanil (Paludrine, see p. 896). This represents a complete departure from any other antimalarial drug. In fowl malaria (*P. gallinaceum*) it has a powerful action on the erythrocytic forms as well as on the pre-erythrocytic (EE forms) in the tissues. In human malaria the action appears to be similar. Its chief advantage is that it is an active prophylactic and suppressant of malaria.

It is moreover easily tolerated and toxic side-effects are few—such as nausea, vomiting and gastric discomforts. In very large doses, as 1 grm., it may very rarely precipitate hæmaturia.

When paludrine is given in 100–800-mgm. daily doses to *P. falciparum* or *P. vivax* gametocyte carriers no effect is observed on the number or microscopic appearances of the gametocytes in the blood, but when given early in the attack, gametocyte production is affected indirectly by checking the primary trophozoite wave before gametogony has occurred. Though gametocytes of both *P. vivax* and *P. falciparum*, when ingested by mosquitoes, undergo exflagellation and fertilization, and may even produce small oöcysts, further development ceases, and it has been shown that complete sterilization of the gut infection of mosquitoes results within 1–2 hours after 150 mgm. of paludrine has been administered to a carrier.

For subtertian malaria the optimum dosage appears to be 100 mgm. three times daily for 7–10 days, but in view of the rapidly acquired paludrine-resistance, Maegraith and others now advocate 600 mgm. daily. For benign tertian and quartan larger doses are indicated, such as 250 mgm. three times daily for the same period, though this treatment does not appear to extirpate *P. vivax* from the circulation any more effectively than does quinine, though a single dose of 100 mgm. is enough to suppress an individual attack. It is generally held that paludrine acts too slowly and has been superseded by chloroquine, etc.

Covell, Nicol and associates (1949) have now concluded that paludrine has a less rapid action than has mepacrine or quinine, so that, in order to prevent relapses in *P. falciparum* malaria, reinforcement with mepacrine or quinine is necessary.

Proguanil resistance.—Proguanil-resistant strains of *P. gallinaceum* have been prepared by Bishop and Birkett and it was found that this character was retained for some months. They also showed that a similar resistance could be produced for sulphadiazine. Similar resistance is found for *P. cynomolgi* in monkeys. In *P. vivax* of the Chesson strain resistance of more than one thousand-fold has been produced by Cooper, Coatney and Imboden (1950). It is suggestive that the antimalarial action of sulphadiazine and sulphanilamide is inhibited by P.A.B.A. (*p*-amino-benzoic acid). The gradual development of resistance in Malaya and Indonesia has been described by Edeson and Field. When first introduced the response to naturally acquired *P. falciparum* infection was good. During 1947 little was found to choose between a single proguanil dose of 100–300 mgm. and a course of 300 mgm. daily for two days. The fever and parasitæmia cleared at the same rate. Since 1948 resistant cases have been frequently encountered and one case out of every four was found to be so. In rubber estates where this condition was found the labourers had been subjected to proguanil suppression for more than two years. When used in mass treatment this resistance is so rapidly acquired that it is transmitted through the mosquito (Seaton and Adams).

V. ACRIDINES (ATEBRIN OR MEPACRINE) AND AZACRIN

Atebrin.—(For synonyms, see p. 874). Atebrin is a bitter acridine dye.

Kikuth originally proved that atebrin exerts a specific schizonticidal action on all malaria parasites, but has no direct action on gametocytes (especially *P. falciparum*). It attacks early trophozoites first, then developmental forms, though if

given over a sufficiently long period, gametocytes disappear. Exflagellation is not interfered with.

The most beneficial effects of atebtrin are seen in the treatment of subtertian malaria and there appears to be little doubt that by its extended use during the recent world war the incidence of blackwater fever has been thereby greatly reduced, though occasionally it may ensue after intensive atebtrin treatment. The results in benign tertian and quartan infections have been less satisfactory.

Atebrin accumulates in the body and stains the tissues and skin yellow. It is stored specially in the liver, spleen and reticulo-endothelium. Elimination is slow and may take a month to complete. The yellow discolouration of the skin may be mistaken for jaundice. The sclerotics are rarely affected, though little correlation has been found between the plasma concentration and therapeutic effect. It has to be distinguished from infective hepatitis, acholuric jaundice, pernicious anæmia and carotinæmia.

Long-continued administration may be associated with an increased incidence of lichen planus (Nisbet and Schmitt, 1945). Other skin lesions have been described, including lichenoid dermatitis, eczematoïd and exfoliative dermatitis. The lichenoid lesions are localized erythematous plaques on dorsal surfaces of hands and feet; subsequently similar lesions have been noted on the mucous membranes. Urticaria has also been recorded. Ginsberg (1946), confirmed by Kierland, has demonstrated the interesting phenomenon that, in persons taking suppressive atebtrin, the finger and toe nails emit a greenish-yellow phosphorescence when exposed to Wood's light (an ultra-violet ray filtered through glass containing nickel oxide). This restricts the passage of all but relatively long wave ultra-violet light (about 3,650 Å). Periorbital eczema with corneal œdema has been reported; after prolonged administration a peculiar brown discolouration of the nails and patchy areas of the palate may ensue.

Another serious idiosyncrasy is cerebral excitation, especially when atebtrin is given in large doses. Some serious cases resemble schizophrenia, especially in some sensitive Europeans, but more commonly in Malays, Tamils, Chinese and Sinhalese (Green, Hoops, Kingsbury).

Atebrin is well borne by pregnant women. Its most valuable property is its efficient schizonticidal action in all forms of malaria.

For small children the daily dosage of 0.08 gm. is best given in milk or concealed in raisins. Atebrin treatment can be combined with 5-10 gr. of quinine hydrochloride daily.

For children the following doses are recommended :

Up to 1 year	.	.	.	0.05 gm. (i.e., half a tablet) daily dose		
From 1-4 years	.	.	.	0.1	"	"
" 5-8	"	.	.	0.2	"	"
Over 8	"	.	.	0.3	"	"

Intramuscular injections are less painful than those of quinine¹. Two injections with an interval of 24 hours are recommended. The soluble form (*atebrin musonate*) is supplied in ampoules containing 0.1 or 0.8 gm. and the contents are dissolved in 3 or 9 ml. of water respectively. In

¹Intramuscular abscesses not infrequently result.

severe subtertian infections its action is not so rapid as is quinine. With the strength of atebirin (0.8 grm. in 9 ml.) the dose is:

6 months to 2 years	1 ml.
2-4 years	2 ml.

gradually increasing to 7 ml. at 15-18 years.

Intravenous injections of 0.2 grm. of atebirin musonate have been given in cerebral malaria, but are not as efficacious as quinine. This amount should be diluted with 9 ml. of water.

An interesting outcome of atebirin treatment in its application to lupus erythematosus by Page (1951). Eighteen cases were treated and one failed to improve. In a few, all lesions completely disappeared within six weeks of commencing treatment and in two associated rheumatoid arthritis also improved.

Azacrin, a compound of the acridine series (see p. 868), in 0.1 grm. tablets, is given in the same manner as atebirin, and is an effective schizonticide in all forms of malaria, especially in subtertian.

VI. PYRIMIDINES AND OTHERS

Daraprim (pyrimethamine) (see p. 870) belongs to a class of compounds hitherto unused against malaria. Its main feature is its extraordinary effectiveness in relation to dosage. Small weekly doses (25 mgm. once weekly) serve to suppress all forms of malaria, and it acts on the parasite at the time of active nuclear division. The pharmacological basis for prolonged antimalarial activity is ascribed by Coatney (1954) to the formation of metabolic products, which accounts for its protection against *P. vivax*. It is a folic acid antagonist preventing nuclear division of the plasmodia, both in man and mosquito (schizonts and microgametes respectively). In doses of 5 mgm. in African children it is as effective as larger ones against trophozoites of *P. falciparum* and *P. malariae*. Daraprim is clearly a powerful schizonticide. A single dose of 0.5 mg. per kg. causes the disappearance of asexual forms of these parasites from the blood. The rate with which it eliminates parasitæmia is quicker than that of proguanil. Its small effective dosage and tasteless character make it the drug of choice in the treatment of malaria in infants and children.

In Malaya, Field, Wilson and Edeson found it failed to eradicate asexual *P. falciparum* parasites. A total dose of 800 mgm. failed to cure 7 out of 26, though East African strains are much more amenable to this drug. There were no failures in patients with *P. vivax* for which it appears most suitable. In Assam and N. Bengal, Gilroy, Norman and Arthur found few failures with single doses of 20 or 50 mgm. and great rapidity of action was observed with *P. vivax*. Giblin in New Guinea (1954) found that *P. falciparum* trophozoites disappeared from the blood in 24-48 hours. Schneider, Canet and Dupoux used it for patients infected with *P. falciparum* and *P. vivax* in Tunisia and Indo-China. They found a single dose of 50 or 100 mgm., or two doses of 50 mgm. effective. Foy and Kondi (1952) have shown that *P. falciparum* gametocytes from a patient treated with daraprim failed to develop to the sporozoite stage in mosquitoes. No toxic side-effects have been observed, though Bruce-Chwatt (1956) has drawn attention to aplastic anæmia which may ensue

after over-dosage and also to a fatal issue in children who inadvertently swallowed a number of tablets. This danger has been overcome by the modern plastic strip pack which prevents them swallowing more than two at a time.

Paludrine-resistant parasites may show resistance to daraprim as shown by Avery Jones in a self-inflicted experiment in Nairobi with a strain of *P. falciparum* imported from Malaya (1953).

Resistance to daraprim is easily acquired. Hernandez, Myatt and Coatney have shown that a 25-fold of resistance is produced in the Chesson strain of *P. vivax* and that this acquired resistance is transmissible through the mosquito. Shute has shown that resistance may be produced in East African *P. falciparum* by single doses of daraprim administered at intervals greater than 14 days.

Thiobismol (sodium-bismuth thioglycollate), injected intramuscularly in 0.2-grm. doses, exerts a peculiar action upon therapeutic benign tertian malaria and produces remissions of 48 hours and is therefore of value in this form of treatment in cases with cardiac embarrassment. After such an injection quinine and atabrin appear to act quicker.

TREATMENT OF BENIGN TERTIAN, QUARTAN AND SUBTERTIAN FEVERS

During a paroxysm of benign tertian it is better to give quinine, chloroquine, camoquine, mepacrine, or paludrine during the rigor or hot stages and not to wait, as formerly advocated, till the patient commences to sweat; but in subtertian malaria, especially, it is wise to commence treatment directly diagnosis is established. Ten grains of quinine (0.1 grm. paludrine or 0.25 grm. chloroquine) should be administered and thereafter in 10-gr. (0.65 grm.) doses three times daily after meals for the next three days (or paludrine 0.1 grm. three times daily). Should the patient be constipated a saline purge should be given, but if he presents severe toxic manifestations, as in subtertian malaria, one should not hesitate to inject quinine intramuscularly or, when signs of cerebral irritation are present, intravenously. The sooner a case of subtertian is energetically treated the less chance there is of relapse or development of pernicious symptoms. It is a wise plan for the patient to take, once a week, a mild saline. For the anæmia, iron and arsenic in pill or tabloid form are of value. For the headache and supraorbital neuralgias which so often follow malaria nicotinic acid is recommended.

For anti-relapse treatment of benign tertian (*P. vivax*), which has always been unsatisfactory, the best results which have now been obtained are by pentaquine or pamaquin, 60 mgm. daily for 14 days. By this method eradication of relapsing *P. vivax* malaria was achieved in 98 per cent., but using only 30 mgm. pentaquine daily (Strauss and Gennis, 1950). Primaquine (see p. 78) has been tested out on American troops with even more favourable results.

Treatment of bilious remittent subtertian malaria, or cases of malaria with intense icterus, should be conducted on the same general lines as for blackwater fever. All solid food should be withheld and sips of glucose solution substituted. Directly the diagnosis is established full doses of chloroquine, camoquine or atabrin should be given, or if the action of these drugs is not sufficiently rapid, an intramuscular quinine

injection. The vomiting may be controlled to some extent by the administration of sodi. bicarb. solution, 1 drm. to the pint, whilst, if the patient is very restless, an injection of phenobarbitone (gr. 5) is indicated. This is specially valuable when there is violent delirium. The antihistamines are useful since they inhibit vomiting and are sedative.

Treatment of cerebral malaria.—The onset of cerebral malaria is to be suspected when the patient becomes drowsy or disorientated. The patient should be nursed in a semi-recumbent position and in severe coma artificial feeding may become necessary. If the systolic blood pressure is 100 mm. or over and pulse volume is good, no time should be lost in injecting quinine dihydrochloride intravenously. This should be performed slowly—at the rate of one minute per grain. This can be repeated after an interval of six hours, till the patient is out of coma, but if the systolic blood-pressure is under 100 mm. and pulse volume is poor, intravenous salines should be given, rapidly at first. Subsequent transfusion of 400 ml. of plasma or glucose-saline by the continuous drip method—40–60 drops per minute—serves to neutralize the toxæmia. In order to bring the quinine into intimate contact with the parasites in the cerebral capillaries, adrenalin, 0.5 ml. of 1:1,000 solution, is injected intramuscularly, sometimes intravenously. Should the coma not clear up within two hours, intravenous quinine must be continued in doses of 6 gr. at six-hour intervals, but not exceeding a total dose of 30 gr. within 24 hours. In experiments with monkeys hyperinfected with *Plasmodium knowlesi*, Maegraith and Devakul have shown that sludging of the capillaries plays a minor part and that the chief factor is peripheral vascular failure. Restoration to normal can be effected by injection with 1-nor-adrenalin (*Levoped*—Bayer Products). Therefore the correct procedure should be injection of adrenalin, followed by blood transfusion and finally chloroquine treatment.

When convulsions are severe oral administration of nembutal or sodium amytal is useful, but, if there is vomiting, resort must be had to injections. In comatose cases which do not clear up, lumbar puncture and withdrawal of 20 ml. of cerebro-spinal fluid may give relief and this should be repeated daily till clinical improvement is noted. Rogan (1944) advised lumbar puncture in every case as cerebro-spinal meningitis may coexist.

It has been pointed out by Marriott (1945) that life is often threatened by asphyxia and dehydration. The former takes place by the falling back of the tongue, gravitation of the saliva into the trachea, and consequent pulmonary oedema. The maintenance of an airway should be the subject of unremitting care. Dehydration quickly arises from reduction of fluid intake by drowsy, disorientated patients who are also sweating profusely.

Ransome, indeed, on these considerations, has made it a routine to nurse his patients in the Fowler position. Beneficial effects are due to gravitational decongestion of the brain, whilst the use of the intranasal, intragastric Ryles' tube for continuous drip hydration and nutrition is a life-saving measure. Central cardiac failure may be treated with strophanthin $\frac{1}{40}$ gr. intravenously and repeated after 18 hours, if necessary. Peripheral failure and oliguria should be treated with caffeine sodium benzoate $7\frac{1}{2}$ gr. every six hours.

Scott (1951) has given his experience with chloroquine and intravenous saline. Chloroquine dihydrochloride was used in 10-ml. ampoules each containing 400 mgm. of base. The contents of one ampoule is diluted with 40 ml. sterile physiological saline. The mixture is aspirated with a 50-ml. syringe. Intravenous injection was made slowly (15 min.), controlled by blood-pressure readings. The smallest dose was 5.8 mgm. chloroquine per kg.; the largest 12.5 mgm. Some were treated by intravenous injection of one ampoule in 500 ml. normal saline by intravenous drip and the therapeutic effect was equally satisfactory.

SUMMARY OF DRUG TREATMENTS OF MALARIA

With the introduction of so many new antimalarial drugs the subjects of treatment and prophylaxis have become somewhat complicated and confused.

Proguanil (Paludrine) and Pyrimethamine (Daraprim) as well as being causal prophylactics in *P. falciparum* infections are effective suppressants in all forms of malaria. They have also the advantage of preventing the completion of sporogony (see p. 885) and of being less costly than the 4-aminoquinolines. Drug resistance may appear and also cross-resistance between pyrimethamine and proguanil. If such resistance is apparent a switch over should be made to chloroquine, camoquine, or mepacrine (atebrin).

Treatment of overt attacks.—Mepacrine (or atebrin) has a rapid action in all forms of malaria, but minor toxic manifestations and psychoses may appear. Chloroquine and camoquine are most effective agents in terminating the attack.

In subjects partially immune.—Single dose treatments with chloroquine, proguanil, camoquine or mepacrine are effective. In view of drug resistance it is wiser to reserve proguanil and pyrimethamine for *prophylaxis* and *suppression*, and to use for therapeutic purposes chloroquine, camoquine, or quinine. If quinine is used for partially immunes, 2–5 days' treatment suffice.

For emergency treatment.—Oral administration is seldom practicable. Antimalarial drugs have to be given parenterally. Quinine is the most effective drug for intravenous injection. It must be emphasized that the lessons it has taught should not be easily put aside. It is a life-saving drug in acute malaria. Mepacrine methane sulphonate, given intramuscularly, is an alternative, but recently has been shown that chloroquine is equally successful, intravenously or intramuscularly, especially as sometimes intramuscular quinine may have disadvantages.

Radical Cure. *P. vivax* and *P. malariae*.—The only drugs effective against the late exo-erythrocytic forms of parasites are the 8-aminoquinolines. Primaquine has been shown to be effective and less toxic than pamaquin. *Mepacrine must not be given* concurrently with 8-aminoquinolines. Treatment with a schizonticide drug (chloroquine) should precede, or accompany, the course of primaquine. The combined treatment is especially applicable when *P. falciparum* is associated with *P. vivax* or *P. malariae*.

In *P. ovale* most infections end in spontaneous recovery.

In *P. falciparum* infections there is convincing evidence against the existence of late E.E. forms of this parasite in the liver. Therefore relapses are due to the persistence of erythrocytic forms and for these reasons any of the more powerful schizonticides, such as quinine, chloroquine or mepacrine will effect a radical cure.

Prevention of Transmission.—The 8-aminoquinolines are the only drugs capable of destroying the sexual forms of *P. falciparum* in the blood. Proguanil and pyrimethamine have the property of preventing these forms from undergoing full development in the mosquito.

Dosage for Causal Prophylaxis Suppression.*Proguanil Monohydrochloride (Paludrine)*

Adults 100 mgm. daily

Children 0-5 25 mgm. daily

Children 6-12 50 mgm. daily

Adults, partially immune, 300 mgm. once weekly.

In Nigeria and W. Africa

Adults 100-200 mgm. daily

Children up to 1 year 50 mgm. 6 times weekly

Children 1-3 years 50 mgm. daily

Children over 3 years 100 mgm. daily.

Pyrimethamine (Daraprim)

Adults 25 mgm. weekly

Children 0-5 6.25 mgm. weekly

Children 6-12 12.5 mgm. weekly.

Chloroquine diphosphate or sulphate

Adults 300 mgm. (base) weekly.

Camoquine (amodiaquine dihydrochloride dihydrate)

Adults 400 mgm. weekly.

Mepacrine hydrochloride (base)

Adults 100 mgm. daily

Adults, partially immune, 300 mgm. once weekly.

Quinine sulphate or hydrochloride

Adults 650 mgm. (10 gr.) daily.

When mepacrine is used, administration should be commenced 14 days before entering the endemic area and the prophylactic regimen continued for one month after leaving it.

Treatment of overt attack

(1) Non immunes.

(a) *Chloroquine*

600 mgm. base followed in 6 hours by 300 mgm. base, then 300 mgm. base daily for 2 days.

(b) *Camoquine*

600 mgm. base, followed by 400 mgm. base for 2 days.

(c) *Mepacrine hydrochloride*

300 mgm. three times daily on first day, 300 mgm. twice on second day, then 100 mgm. three times daily for 5 days.

(d) *Quinine sulphate or hydrochloride*

1,000-1,500 mgm. (15-20 gr.) daily for 2-5 days.

Emergency treatment.—(1) *Quinine dihydrochloride* 650 mgm. (10 gr.) in sterile saline intravenously, repeated in 6 hours, if necessary. *Not more than 3 injections in 24 hours.*

Use distilled water if total volume does not exceed 10-15 ml. Give slowly at rate of 1 gr. per minute.

(2) *Mepacrine methane sulphonate*.—375 mgm. (or mepacrine hydrochloride) intramuscularly; repeated in 6 hours if necessary.

(3) *Chloroquine salts*.—*Chloroquine diphosphate*, or *hydrochloride*, *intramuscularly*, 200-300 mgm. base (in ampoules), repeated in 6 hours, if necessary. Intravenously 400 mgm. base in 500 ml. normal saline by *intravenous drip* over a period of one hour. *Chloroquine sulphate* (nivaquine) is supplied in 5 ml. ampoules (40 mgm. base to 1 ml.) and is given in dosage of 200 mgm. intravenously, repeated after 8 hours if necessary.

Radical Cure of *P. vivax* and *P. malariae* Malaria

- (1) *Pamaquine naphthoate*, 8–10 mgm. base, three times daily, for 10–14 days.
- (2) *Primaquine diphosphate*, 15 mgm. base, for 14 days, or 7 mgm. base, three times daily for 14 days.

(Careful supervision is necessary over patients taking 8-aminoquinolines, because of unpredictable occurrence of acute intravascular hæmolytic with, or without, hæmoglobinuria).

PROPHYLAXIS OF MALARIA

Anti-mosquito measures.—It is obviously impossible to wage war on all mosquitoes. Modern anti-malaria measures are based on the belief that it is more economic and effective to concentrate on the main malaria-carriers in each particular district—a procedure known as *species sanitation*. Some varieties enter dwellings and show preference for human blood and are said to be *anthropophilic*, but the majority are *zoophilic* and prefer to feed on domestic animals (*see* Appendix, p. 1044).

The *precipitin test* is employed for the precise determination of the blood, human or mammalian, upon which captured anophelines have fed. The stomach blood is squeezed out on to filter paper, and rubbed well in. The paper should be divided into eight sectors, and blood drops disposed at the periphery and as such can be stored for as long as 3–4 months in a dry place. Then sensitized sera, suitably diluted, are placed into tubes containing 3 ml. of saline and the filter-papers containing the dried blood added. A positive reaction is shown by the development of an opalescent ring at the point of contact; it may appear at once, or after incubating at 37° C. Tubes should be inspected at ten-minute intervals up to one hour. Control tests should be performed.

Other factors in planning antimalarial measures govern the principles. The distance between breeding places and dwellings is known as *distance of dispersal*. In the Oriental region a zone of half-a-mile radius free from breeding-places is found enough to protect a dwelling, but in the Ethiopian region this must be more extensive. Formerly it was thought that, generally speaking, about a thousand yards or one mile between a ship and a malarious shore would secure protection for the crew, but this does not always suffice, because Kligler has shown that, aided by prevailing winds, and especially during hibernation flights, the mosquitoes may travel five miles.

Aragão and colleagues (1953) are using modern methods of radioactivity for estimating flight range. Larvæ of *Anopheles* (*Kerteszia*) were collected from breeding places in Bromeliads and bred out in artificial containers containing 1:10,000 thorium nitrate. The radioactive element was detected in adult mosquitoes captured far away. The method of detection involved incineration of the mosquitoes and autoradiographic determination of the trajectories of *alpha* particles after 30 days' exposure of the remains against photographic plates.

Killing off adult mosquitoes.—Light airy houses with plenty of ventilation, and with no dark corners, discourage the entry of mosquitoes; in the tropics most of the adult insects gain entrance and suck blood during the night. Swatting the resting insects perched on ceilings or walls of dwelling-rooms has been found very effective against *A.*

atroparvus, especially in Holland. Spraying the walls with an insecticide (Pyrethrum—Flit) once or twice a week has been found useful in India against *A. culicifacies*, especially during the autumn months and in cool weather. The "Freon bomb," a small round drum, containing pyrethrum and DDT concentrate dissolved in dichlorofluormethane, has been evolved by American Army hygienists especially for bedrooms. On opening the nozzle the insecticide is blown out and forms a fine fog, or aerosol, which is projected 6-8 feet, killing all mosquitoes in 100,000 cubic feet. Residual DDT spraying kills off anopheline mosquitoes (*A. darlingi* and *A. aquasalis*) which are anthropophilic as well as domestic (Giglioli) (see Chap. LII).

Principles of species sanitation.—In this procedure measures are taken to prevent the breeding of dangerous species of mosquitoes; they must therefore be based upon an intimate study of the habits of each. These measures may entail drainage of swamps, if they can be incriminated, but they seldom can. In some cases it is more important to fill in holes and borrow-pits, to camber roads to prevent puddles, and to train the bends of streams or flush them periodically. Marshes, open to the sea, can be periodically flooded with salt water which kills off the larvæ.

In some species of the *Anopheles funestus* group, and especially for *A. minimus*, shading of streams prevents breeding, but in this case the amount of overhead cover must be thick enough to prevent the growth of grass.

To prevent mosquito breeding in *streams* and *waterways*, it is necessary to get as even and swift a flow as possible without eddies or backwaters. The stream should be canalized, that is to say, the sides should be sloped at an angle of 45 degrees. Embankments should be lined with large stones and the vegetation cleared from the edges. During the monsoon it is especially important to prevent the formation of pools after the subsidence of extra high flood. A stream thus treated is practically self-sterilizing, except with a species of anopheline, such as *A. maculatus*, which is specially adapted for life in rocky waters. If necessary, canalization should be supplemented by oiling. Subsoil drainage can be employed in place of canalization and, indeed, forms an important feature of estate sanitation in Malaya. Flushing streams with automatic siphons is a modern method.

Seepage, or infiltration of water through bunds or dykes at the bottom of a hill foot, usually forms a fruitful breeding-ground for anophelines. *Running swamps* in the course of a stream in level country may form dangerous breeding-spots. They can be dealt with by oiling or Paris green. *Borrow-pits*, formed usually in the process of railway construction, may, when several years old, form suitable breeding-places. *Tanks*, in India and Ceylon, are seldom dangerous, but, if the margins are much overgrown with vegetation, certain anophelines may obtain a foothold.

Rice fields are dangerous when the water is kept in continuous motion through the fields; uncultivated plots in terraced fields that are allowed to become flooded are especially so. In Java the drying-off of the fields throughout a tract on one day each week has been made obligatory and is efficacious without apparently damaging the growth of the rice. To the inexperienced eye there might seem enormous potentialities for breeding anophelines in paddy fields, but the fields themselves are not always so much to blame as irrigation ditches.

Mangrove swamps, especially in the Andaman Islands and West Africa, are associated with virulent malaria due to the breeding of certain species of

anophelines, especially *A. ludlowi* (*sundaicus*), and *A. gambiae* var. *melas*, in saline water. Sunlight also is necessary for the development of these larvæ. Thus, the dense virgin mangrove forest is healthy so long as it is daily traversed by tides; but when trees are cut down, or when bunds are constructed to interfere with tidal movements, and derelict pools are formed which are gradually diluted by rainfall to a suitable salinity, the breeding of anophelines takes place. Drainage is difficult at sea-level unless there is a big tidal range. In Malaya, owing to the sixteen-foot drop in the tides, it has become possible to install automatic sluice-gates to the bunds.

Smaller collections of water, if overlooked, may constitute a grave danger. A sagging gutter may hold enough water to support large numbers of larvæ; moreover, a good deal of atmospheric moisture is condensed upon the roofs of tropical bungalows so that the gutters are constantly being replenished, even in the absence of rain. Holes in rotten trees may breed a limited number of anophelines; indeed one European species, *A. plumbeus*, breeds exclusively in this situation. In tropical Africa, *A. gambiae*, the most active vector in the world, breeds in collections of water, small or large, of the greatest diversity. The most trivial road puddles, hoof marks or seepages may contain larvæ, as well as the larger collections. *Wells* are a certain source of trouble where they are built within native houses and where, in the absence of light, species of anophelines have adapted themselves. In Palestine and Macedonia they have been found to be the main breeding-place of *A. claviger* (*bifurcatus*).

Oil.—Oiling kills mosquito larvæ probably in several ways, but mainly by suffocation and its toxic action. The rapidity with which larvæ die depends upon the volatility and toxicity of the oil. The oil enters the spiracles of the larvæ as they break through the film, in order to reach the air and penetrates to varying distances according to the amount which has entered. When the tracheæ are full of oil, death occurs within twenty-four hours. The main determining factor is the presence of toxic substances, such as aromatics present in the oil (Jones, 1951). Its spreading power can be improved by the addition of 1–2½ per cent. of castor or coconut oil. In Palestine Kligler found the most effective mixture to be 1 part of crude oil to 4 parts of kerosene, with the addition of 0·1–0·2 per cent. castor oil. *Anti-malarial oil* (A.M.M.) is a mixture containing diesel oil, solar oil and kerosene put up by the Asiatic Petroleum Co. Diesel oil is unrefined, and is added to give a lasting effect. *Malariol* is an approved mixture of petroleum impregnated with DDT to 5 per cent. (it is reasonable to expect now that all anti-larval oils should include DDT), with which a film is formed on the surface of the water.

The following conditions are postulated for anti-larval oils as far as film stability is concerned:

- (1) The main point should be quick penetration of the respiratory siphons of the larvæ—in not more than ten minutes.
- (2) The oil should exert a direct toxic action on the larvæ and should change the flora of the streams.

The oil may be applied to the water in several ways. Spraying consists of forcing the oil under pressure through an atomizing nozzle from a special machine. Of the various patterns, the "Kent" sprayer best suits the capacities of the tropical labourer. Sprayers should be fitted with leather or flexible metal adjustments, as petroleum oil perishes rubber in

a few days. For road-side ditches oil carts may be used, but for all purposes the knapsack sprayer is the most adaptable. The best oil for the purpose is a heavy oil which will issue from the sprayer as a fine cloud and spread uniformly over the water. Oil swabs, or cotton-wool steeped in oil and weighted down by a stone, when thrown into water, are ideal for rock springs and running streams. In certain malarial districts in the United States oil-soaked sawdust has been found to give a more complete

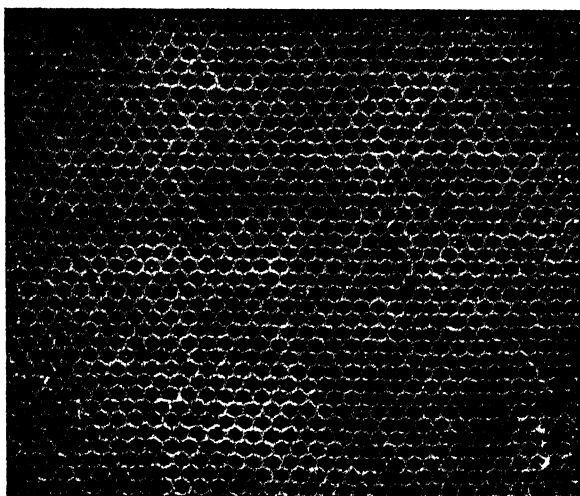


Fig. 11.—Mosquito-netting, 25/26 holes to the sq. inch.
(MacArthur, *Jl. R.A.M.C.*)

and permanent oiled surface and has the advantage of being easily transported. The oil gradually exudes and spreads as an even film over the surface of the water. In Panama drip cans and barrels are used from which the oil constantly drips from cork wicks or through holes from which nails project, but their value as an oiling agent is less than that of sprays. Oil must be applied at *seven-day intervals*.

For modern methods of malaria prophylaxis by DDT, and other insecticides, see Chapter LII. By these methods malaria has been virtually eliminated from the United States, Italy, Sicily, Sardinia, Corsica, Crete and Cyprus. The incidence of malaria has decreased greatly in Brazil, Venezuela, Madagascar and N.E. Australia. It is absent from Argentina and Chile. In large areas of Bombay, Mysore and Ceylon modern control has almost completely prevented the infection of man.

Larvivorous fish of some suitable local or well-known foreign species can be introduced. Favourites are the "millions" ("Millions-fish"—*Lebistes reticulatus*—of the Indies), or "top minnow," *Gambusia*, which is a surface feeder, capable of withstanding heat and cold, and also viviparous and cannibalistic. In pools, weeds must be cut away to give the fish access to the larvæ. This method is efficacious in temple wells and pools in

Bombay against *A. stephensi*, and in the Adriatic Islands against *A. maculipennis*. In Java, by the introduction of a fish (*Puntius javanicus*) which feeds on water-plants, the breeding of anopheline larvæ has been frustrated.

Mosquito-netting.—Mosquito-netting should contain 25 to 26 holes to the square inch (Fig. 11). The best is known as "bobbin" netting, woven of 80's cotton (by which is meant that 1 lb. of the thread will reach 80 times round a circumference of 840 yards). The square inch of the trade does not correspond to that of the mathematician; it means that the count is made along two lines of holes which fall within the opening of one inch square. Therefore, there are some 150 holes to the square inch (Fig. 12).

The main points in efficiency are that the holes should not be too large; that the net should not be so narrow as to permit knees and elbows to be bitten

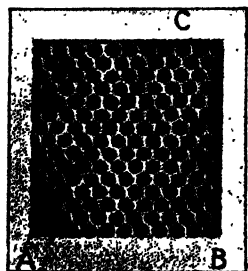


Fig. 12.—The correct method of counting the mesh of cotton netting. The mesh of this net is the sum of the counts made along the lines A B and A C, the hole at A being counted twice. (MacArthur, JI. R.A.M.C.)

through the netting, and that the sides should be deep enough to be tucked in securely. When two single beds are used occupants can be protected efficiently as follows:—The beds are placed close together and the intervening space covered with a single sheet, placed immediately over the mattress and beneath the other two sheets. The net itself should be suspended from the framework, or attached by tapes to rings hung on three wires and stretched across the room. When a mosquito is found inside the net it can be destroyed with ease by passing a lighted candle downwards about three inches from the insect when it will fly back into the flame. If the edges of the net are not tucked in, they must be so weighted that they touch the floor, so that the insects cannot crawl underneath.

During the daytime the net should be rolled up so that it contains no mosquitoes when set up for the night. Light attracts mosquitoes.

Application of dimethyl phthalate to wide-mesh nets.—The aperture may be $\frac{1}{2}$ inch square and easily penetrable by mosquitoes; but, if netting is impregnated with this repellent, it will exclude the pests.

Screening of houses and barracks and other institutions by wire gauze is widely practised, especially by the Americans in Panama. The windows and doors are covered with wire gauze of a mesh fine enough to exclude mosquitoes; 14 mesh screencloth of 30 I.S.W.G. will suffice in most districts, but for *A. minimus* a 16 mesh of 28 I.S.W.G. is necessary. In the former case the wire is 0.0124 in. in diameter and the aperture measures 0.059 in. Of the various metals used in the manufacture of screencloth, an alloy called Monel metal is the best and does not corrode in a damp climate.

Mosquito boots of soft leather or canvas—or Wellington boots—protect the ankles and legs in the evening; for ladies, a pillow-case drawn up over the legs and feet is a useful precaution. *Anti-mosquito veils and gloves* (or gauntlets with sleeves) are used to protect soldiers and others on night duty.

REPELLENTS.—Earlier repellents to which objections were raised have been replaced by a mixture of synthetic substances such as Indalone, 20 parts, Rutger's 612, 20 parts, and dimethyl phthalate, 60 parts. The issue is 2 oz. weekly for each man. During a shortage of other constituents (D.M.P.), dimethyl phthalate, gives the best results (*Sketofax*, B. W. & Co.'s proprietary preparation, is also based on D.M.P., as is also Dimeepol which contains, besides D.M.P., ethylhexandiol emulsified in a vanishing cream). During the hours of darkness the face and hands should be treated, but it should be kept out of the eyes. During the daytime it is necessary to repeat the application two-hourly. Where mosquito nets cannot be used, repellent fluid is used to impregnate headveils, sleeves and oversocks. These overgarments are made of fine string "fish-netting" which acts as a vehicle for the repellent. The impregnated netting is carried in a waterproof wallet with a cloth lining and re-impregnation is effected by soaking the cloth-lining once a week with $\frac{1}{2}$ oz. of repellent lotion. One drawback is its solvent action on plastics, especially artificial silk. Dibutyl-phthalate is similar, more persistent, but is less rapid in action.

Stearin cream gives 97 per cent. protection for eight hours. It is not greasy, but unstable.

Stearin	16 per cent.
Water	69 " "
Glycerin	4 " "
33 per cent. ammonia in water	0.9 " "
Pyrethrum extract 2% total pyrethrins	10 " "

A new repellent is diethyl toluamine which has been tested in Tanganyika against *A. gambiae* by Gilbert and others (1956). The technical grade contains 70 per cent. of meta-isomer and is better than the ortho-isomer. It is specially suitable for garments.

PROPHYLAXIS OF MALARIA

The following terms must be defined:

(a) *Gametocyte prophylaxis*.—Prevention of infection by the mosquito on account of the action of drugs on the gametocytes or their precursors in the human body.

(b) *Causal prophylaxis*.—Prevention of infection by human host through the action of drugs on the sporozoites or upon intermediate stages of the malaria parasites in the body.

(c) *Suppressive prophylaxis*.—Prevention of development of clinical manifestations of sub-patent infections by means of the action of drugs on the asexual forms.

Chemoprophylaxis.—*Quinine* prophylaxis has been practised by most residents in tropical countries for many years, but it has always been an open question whether its protective value had been definitely proved. It has been superseded by newer and more efficient preparations which lack the unpleasant side-effects of "cinchonism."

Paludrine (proguanil) appears to be a good causal prophylactic in that it does not prevent penetration of sporozoites into the skin, but destroys the pre-erythrocytic stages (E.E. forms) of the malaria parasites. It is, moreover, non-toxic. The dosage is 0.1 gm. daily for 10 days as causal prophylactic. Daily dosage appears essential. It is more effective in subtertian than in benign tertian and prospective travellers should take 0.1 gm. paludrine for at least 10 days before entering a malarious country and for a similar period after leaving it.

Daraprim (pyrimethamine), given weekly in a dosage of 25 mgm., afforded complete protection against overt malarial attack in a group of 14 non-immune subjects repeatedly exposed to mosquito infection (*A. stephensi*) by a West African strain of *P. falciparum*. The action appears to be that of a true causal prophylactic against this species of parasite. The advantages are self-evident. This drug acts on the plasmodium at the time of nuclear division. Its destructive action on the malarial oöcysts is seen as early as two hours and as late as 144 hours after administration, and this is proof that it plays a decisive part in limiting malarial transmission (Shute and Maryon, 1954).

Atebrin (mepacrine).—It acts more as a *suppressive* than as a *causal* prophylactic. For the latter, in order to be completely effective, the dosage ranges from 6–8 gm. given over a period of 22 days before, and some 30–60 days after, exposure to infection.

The important factor in suppressive prophylaxis is the *atebrin level* of the blood. To be effective this should be between 25–30 microgrammes (γ , or 0.001 mgm.) per litre of plasma, or 2.3–3 γ per 100 ml. (25 ml. of blood are required for the test). Under active service conditions in troops, this level is much influenced by sweating or by too rapid elimination in the urine. It seems that, when once this level has been lowered, malarial infection can break through and parasites may appear in the blood in large numbers, but if atebrin is then given in therapeutic doses (0.6 gm. initial dose, followed by 0.3 gm. daily), the trophozoites once more disappear.

Inoculated or therapeutic malaria.—Following the work of Wagner-Jauregg of Vienna, the treatment of general paralysis of the insane and other grave nervous disorders includes the injection, subcutaneously or intramuscularly, of 1 to 2 ml. of blood containing benign tertian parasites, with consequent production of attacks of malaria in the person thus injected. The best results are obtained with blood which has been immediately defibrinated and kept in a thermos flask at freezing-point. It is most important that *P. vivax* and *P. ovale* strains should be used; deaths have occurred from inoculation with certain strains of *P. falciparum*, though others in James's hands proved beneficial. Favourable results have been recorded in Vienna from the employment of *Spirochaeta duttoni* of relapsing fever in place of malaria.

The preservation of the malaria parasites by freezing and maintenance at low temperatures has been demonstrated, but the asexual forms of the plasmodium have been used. Now Jeffery and Rendtorff (1955) have succeeded in preserving viable sporozoites of all species of human malaria at under -70°C for as long as 375 days. Some 37 trials of frozen sporozoite material resulted in 30 successes. It is possible by the method also to preserve asexual parasites in blood for as long as 404 days. A combination of these methods has given good results. This is a practical and successful method of distributing infective material over long distances.

Therapeutic malaria may also be produced by the bite of an infected mosquito or by the actual subcutaneous injection of the extract of the salivary glands containing sporozoites. Contrary to the opinion formerly held, it has been shown that inoculation of sporozoites from the salivary glands of one infected anophelis will produce in some persons *quotidian* rigors due to parasites sporulating within a day of each other. In many cases, also, after an incubation period of 7–10 days, the onset of the malaria attacks is characterized, not by typical

intermittent fever, as seen in Charts 1, 2, but by a *remittent* fever which may persist for a week or more before becoming frankly *intermittent* (Chart 5). This feature appears to have been noted in the historic inoculation experiments originally carried out by Manson and Grassi. Kitchen and Putnam (1946) describe the onset as characterized by a few days of continuous-remittent fever, quotidian or tertian intermittent, or by a combination of both. Regardless of type of onset most *P. vivax* attacks commence and continue with quotidian periodicity. One objection to the use of benign tertian malaria is proclivity to quotidian fever, which is extremely exhausting to debilitated patients. Injections of thio-bismol, 0.2 grm., have been shown by a number of observers (Schwartz, Brunsting and Love, Cole, Whelen, and Shute) to have the property of destroying the half-mature schizonts of *P. vivax*, thus eliminating alternate cycles, and of transforming a quotidian into a tertian fever. (Thio-bismol is the trisodium salt of bismuth thio-glycollic acid— $\text{Bi}(\text{SCH}_2\text{COO Na})_3$ —and contains 38 per cent. metallic bismuth.) The optimum time for injections is about the fourth day. During the incubation period it has no effect; a similar effect has been shown on quartan by Kaplan (1946).¹ The results of therapeutic malarial treatment have, according to Yorke and Macfie, been favourable.

In inoculated infections disinfection by quinine, paludrine, chloroquine or atabrin is extraordinarily easy. To effect a complete cure, the amount of quinine administered varies from 45–150 gr. and about 3 grm. of atabrin. Relapses after subcutaneous inoculation with B.T. quartan or ovale after treatment are almost unknown, while in naturally-acquired malaria they are common. It seems, therefore, that malarial infection produced by the injection of sporozoites is much more long-lived and much less amenable to quinine and can now be explained

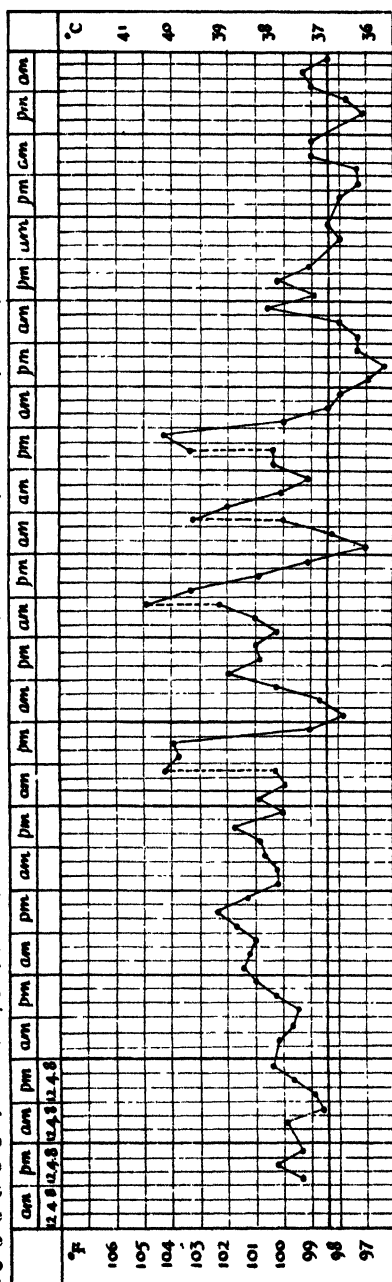


Chart 5.—Inoculated benign tertian malaria, showing initial remittent pyrexia. (Dr. G. C. Low.)

¹ Injections of neocarphenamine have a similar effect.

by the existence of E.E. forms in the liver. Valuable information about the failure of quinine to act prophylactically has also been obtained. The administration of quinine in 10 gr. solution daily for five days before, on the day of, and eight days after the bite of infective mosquitoes fails to prevent the development of malaria; similar results have been obtained in cases where 30 gr. in solution were given on the day of feeding infective mosquitoes and on each of the two following days. These experiments show that quinine has no action upon sporozoites injected by the mosquito, and they remain virile after immersion in quinine suspensions 1 : 2,500 for four hours; on the other hand the development of malaria can be prevented by 10 gr. of quinine daily taken for ten days after the infecting bites, but this does not prevent long-term relapses.

In America it has been shown by Young, Eyles and others (1955) that American Negroes are not only insusceptible to *P. vivax* of American origin, but also to strains from all parts of the world, while Butler and Saperro have proved that this refractoriness cannot be overcome by massive doses of the infecting parasites.

Nephrosis treated by malaria.—The effect of inoculated malaria on nephrosis is essentially the same as that of A.C.T.H. Nephrosis, in its earlier stages, may be reversed by these means. In one instance A.C.T.H. did not provoke a remission, although malaria subsequently did. Lipoid nephrosis is also favourably influenced and the œdema is cleared up by diuresis (Gairdner and Byrne, 1952).

Gairdner and Shute (1955) have reported upon the results of this treatment in 65 cases, of this number 51 had pure nephrosis: 14 (28 per cent.) of these achieved remissions lasting longer than 3 months, 12 (24 per cent.) subsequently remained well for 6 years. No lengthy remissions occurred among 14 cases of nephritic nephrosis.

The only common complication was anæmia, but malaria has its place in treatment since long-standing remissions can be induced in about 1 in 4 patients with pure nephrosis, sometimes after cortisone has failed.

CHAPTER V

HUMAN TRYPANOSOMIASIS

Definition.—Diseases produced by parasites of the genus *Trypanosoma*, characterized by irregular and chronic fever, skin eruptions, local œdema, adenitis, physical and mental lethargy, and sometimes death. The trypanosome is spread by the tsetse flies (*Glossina*) in Africa, and by winged bugs (*Reduviidæ*) in Central America.

The trypanosomes are blood parasites which are widely distributed in animals, especially in big game, in the countries in which these diseases occur. These animal hosts act as reservoirs of the trypanosomes which cause disease in man. The geographical distribution of African human trypanosomiasis is shown in Map I; that of the South American in Map II.

I. AFRICAN HUMAN TRYPANOSOMIASIS

Geographical distribution (Map I)—The distribution of human trypanosomiasis (sleeping-sickness) corresponds roughly with that of the tsetse flies, *Glossina palpalis*, *G. tachinoides* and *G. morsitans*. It is found in scattered areas in French W. Africa, on the Gambia, in Sierra Leone, the Gold Coast, Nigeria, Cameroons, the Southern Sudan, and Uganda; but its main stronghold is along the waters of the Congo and its branches. The most southerly focus in Africa has been found in the Okavango and Chobe swamps in Ngamiland, on the borders of the South African Union. Rhodesian sleeping-sickness is mainly confined to East Africa. The magnitude of this problem can be gauged from the fact that the tsetse fly inhabits 280,000 sq. miles out of a total 640,000 sq. miles of East Africa alone. During the last 25 years preventive measures have produced a net gain of only 3 per cent. in land permanently cleared of the fly. This "fly country" of unused and uneroded land may soon be needed when the human population rises beyond the capacity of the present settled regions to support it. As the role of animals as reservoirs of *Trypanosoma gambiense* and *T. rhodesiense* is still in doubt the need to clear these matters up is pressing. For detailed information on this and many other matters on this subject the reader is referred to "The Natural History of Tsetse Flies" by P. A. Buxton (1955). The following is a detailed summary of the known distribution:—

Distribution of Sleeping Sickness (Trypanosomiasis) in Africa

In French West Africa.—*T. gambiense* prevails. *G. palpalis* and *G. tachinoides* are vectors.

Senegal to 30 miles North of Dakar (Sangalkam).—In South Casamance, Siné-Saloum and on Minor Coast.

French Guinea.—Labé Mamou in Fouta Jalon and in forestal regions South and West of Kissidougou and North Guéckédou.

French Sudan.—Along Bani River. Smaller foci near Black Volta River, South of Bamako, along Niger and tributaries, Senegal River and tributaries.

Niger.—In extreme South on Niger River between Say and Boumba, district of Tamou.

Ivory Coast (Upper).—Ouagadougou, Koudougou, Yako, Bobo-Dioulasso, Banfora, Gaoua, Diebougou, Batié Kampta.

Ivory Coast (Lower).—Province of Man.

Dahoméy.—Tanéka-Koko, Dompago, Djougou Division of Parakou Province.

Togo.—On border of Dahomey, North East of Sokodé.—Banks of Binah, Kara, Pakélou, Poundja and Zinah Rivers.

Portuguese West Africa (Angola).—North districts of Zaire, Congo, Cuanza, and Lunda. Coastal districts at Benguela, Lobito, and Egito. *G. morsitans* found in East Angola.

Portuguese Guinea.—Mildly endemic, *G. palpalis* and *G. submorsitans* widespread.

Islands of San Thomé and Príncipe.—Introduced from Angola in 1907. Repressive measures—slaughter of wild pigs. In 1915 Príncipe free from trypanosomiasis.

Spanish Guinea.—Utamboni, Muni Rivers in South, Beni River in North, Estuary of Benito River and Aye River.

Island of Fernando Po.—*G. palpalis* common. In 1919 trypanosomiasis was widespread.

Liberia.—In East Province between St. John and Sangwin River. In 1940 epidemic in Kissi tribes.

British West Africa

Gambia.—North Bank Province in Lower Baddibu area: South Bank Province—Bintang-Bwiam, Kanfinda-Sintet areas, also Bathurst, Kombo St. Mary Province, MacCarthy Island, and Upper River Provinces. *G. palpalis*, *G. tachinoides* and *G. morsitans* common.

Ghana.—Number of cases increased since 1925—favourable conditions produced by deforestation. Highest incidence—Kumasi, Beikwai, Yendi, Gambaga, and Navrongo.

In Northern Territories, in Burifoo, Nadawli, border area between Lawra and Tumu, South Mamprussi, Kusasi and Kamba valleys.

Sierra Leone.—Endemic on Sherbro Island. Chief zone is Kailahun district in Kissi tribe.

Nigeria.—Infection rate 2.2 per cent. Central—Zaria, Niger Province, South part of Katsina and Kano, parts of Benue, Bauchi and Plateau Provinces. Recently South Division and Jemaa.

In North *G. tachinoides*; in South *G. palpalis*, *G. morsitans* and *G. submorsitans*.

Cameroons (Mandated Territory).—Along tidal creeks, up Mongo River in the Tiko area. In Cameroon Mountains, 20–40 per cent. of natives infected.

French Cameroons.—Upper Nyong focus is cradle of disease. In West region two centres are Noun and Mungo.

French Equatorial Africa.—Well distributed; chief centre, Moyen Congo.

Gabon.—In Estuare department S.S. has increased since 1933, especially at Libreville, also in districts of Nyanga, Ngounié, Woleu-N' Tem, Ogooué-Maritime, Adoumas and Djouah.

Moyen-Congo.—Haute-Sangha near South East boundary—subdivision of Nola—most severely infected areas in Equatorial Africa—20 per cent. infected, also subdivision of Sibiti, in Niari and the Dongou subdivision in Lower Oubangui area.

Ubangi-Shari.—Ouham worst infected department, also Kemo-Gribingui.

Foci also in Zémio and Obo in Haut M' Bomou, Lobaye, Ombella-Mpoko, Ouham-Pende, Ouaka, and Basse-Kotto.

Chad.—Moyen Chari along the main river in South West, in Niellim district, to North West in Logone, in subdivision of Moundou and Doba, in Baïbokoum, and focus in Kasser canton between Fort Lamy and L. Chad.

Belgian Congo.—Uneven in all provinces. Large areas free in centre North and North East of Stanleyville, on Katanga plateau to the South. *T. gambiense* prevalent, but *T. rhodesiense* suspected in Bukania. In province of Léopoldville, along Congo to Kwa, along Kasai River, in Kwango to Moyen Wamba and East to Kwilu. Province of Lusambo vast endemic area. In Province of Coquilhatville S.S. is regressing, in Stanleyville stationary. Region of Lake Albert has remained free from infection for five years. In Costermansville results of control favourable, but large foci still remain along Lualaba, and Kongo-Kindu railway. In Province of Elizabethville increase of endemicity on the Lualaba, but some regression on L. Tanganyika.

Ruanda-Urundi (Mandated Territory).—Notable regression in recent years. Infected areas confined to narrow strip below 11,000 metres along Ruzizi River, bordering the East shore of L. Tanganyika.

Anglo-Egyptian Sudan.—Confined to South district of Equatoria Province where *G. palpalis fuscipes* is found. Foci are Tembura in the Zande district of the Yubu River close to the West border of French Sudan. *G. morsitans* in Nuba Mountains : *G. submorsitans* and *G. palpalis* on Yubu and Sueh River.

British East Africa

Uganda.—S.S. appeared in epidemic form on shores and islands of Lake Victoria in 1900 ; reduced population of 300,000 to one third. Epidemic arrested by removal of population. In 1919 milder epidemic in Madi district of the Albert Nile and spread to West Nile district. Now West Nile and Koich River area chief foci. Minor foci in Gulu, Madi and Chua districts, and in Lake Edward-George area. In 1941 cases discovered at some distance from Lake Victoria, probably due to *T. rhodesiense*. In 1942 small epidemic in Busoga district spreading to Central district and across Kenya border. Buvuma Island, South of Jinga, also infected. Investigations suggest that here *G. pallidipes* is the main vector of *T. rhodesiense*. Other species *G. palpalis*, *G. morsitans* and *G. fusca* are of less importance.

Kenya.—S.S. introduced from Islands of Lake Victoria and reached South Kavirondo in 1906. Now found in Central and South Kavirondo districts of Nyanza Province, mostly in Kadimu, Uyoma, Semie, Port Victoria and Kania-doto. *T. gambiense* chief parasite, *G. palpalis*, chief vector, also *G. swynnertoni*. In South Kavirondo *G. brevipalpis* and *G. pallidipes*. *T. rhodesiense* recently proved in scattered areas.

Tanganyika Territory.—Up to 1922 *T. gambiense* was trypanosome recognized and *G. palpalis* vector. From that time Rhodesian type recognized East of Mwanza where *G. morsitans* and *G. swynnertoni* abound. 1938–1940 increasing number of cases in North Province. At present S.S. found—Central Province—Singida ; East Province—Ulanga ; Lake Province—Mwanza, Musoma, Biharamulo ; South Province—Liwale, Masasi, Tunduru, Songea ; West Province—Kahama, Tabora, Kigoma, Ufipa ; South Highlands Province—Chunya. Eleven fly-belts are recognized. Great Western belt extending North West to Uganda border and South West to South end of Lake Tanganyika ; Great East belt passing to Portuguese East Africa and North to Kenya. *G. morsitans* found in half the territory. *G. swynnertoni* in North zone in thorn woodland. *G. pallidipes* widely dispersed in pockets.

Nyasaland.—In view of numbers of tsetse small numbers of cases of S.S. surprising. Infected areas in Kota Kota in South Nyasa. *G. morsitans* widespread. Trypanosome is *T. rhodesiense* of reduced virulence.

North Rhodesia.—In North trypanosome is *T. gambiense* conveyed by *G. palpalis*. In South it is acute Rhodesian type—*T. rhodesiense* conveyed by *G. morsitans*. Increase in 1935 near Mumbwa to West of Livingstone—Broken Hill Railway. Luangwa Valley constitutes endemic focus. Gambian form in the extreme North in Abercorn district, near shores of Lake Tanganyika, mainly in village of Mbete.

South Rhodesia.—*T. rhodesiense* S.S. near Busi River in Sebungwe district. In 1942 cases discovered near Chirunde on the Zambesi River in the Lomagundi fly-belt. Main tsetse in *G. morsitans*.

South Africa—Bechuanaland Protectorate.—In Ngamiland in North S.S. (local name Kgotsela) known since 1908. Tsetse belt in Okavange and Chobe swamps. Trypanosome—*T. rhodesiense* and *G. morsitans* vector. Now chief focus is Tsau-Gwedau area.

Portuguese East Africa—Mozambique.—S.S. due to *T. rhodesiense* on shores of Lake Nyasa. *G. morsitans*, vector, is widespread over area bounded by Lake Nyasa in West, Rovuma River in North, and Lucholingo River in South East. In South Catur and Madimba.

Abyssinia.—S.S. thought to exist in low country South and West of Addis Ababa. *G. palpalis* and *G. morsitans* occur along tributaries of Acobo and Chibise Rivers. *G. pallidipes* also. (For illustrations of tse-tse flies—Plates IV and V).

GAMBIENSE SLEEPING SICKNESS

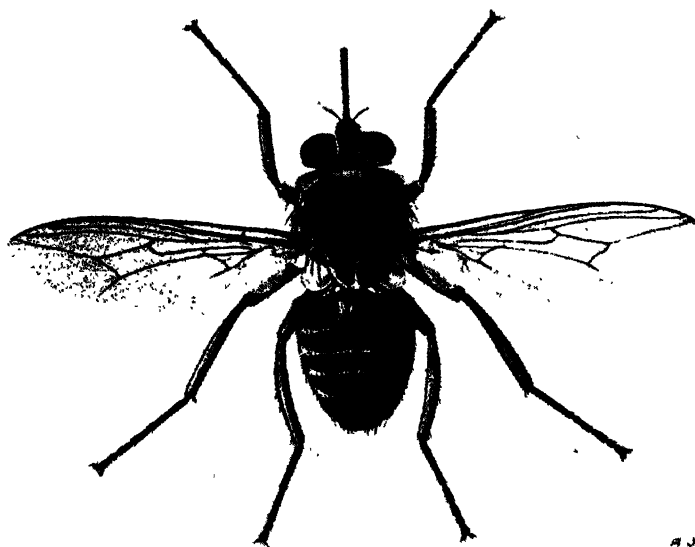
Ætiology.—Neither age, sex, occupation, nor race *per se* has any influence on the susceptibility to trypanosome infection, except in so far as those factors conduce to opportunity. Thus, Schwetz found a baby of twenty days old infected in the Belgian Congo. Occupation (boatmen, fishermen, water-carriers) conduces to infection, if it entails frequenting the waterside haunts of the glossina. In common with other trypanosomes, *T. gambiense* (Fig. 18), as seen in fresh blood, is an active, wriggling organism, having a spindle-shaped body which is slightly compressed laterally and spirally twisted. Dividing forms are sometimes met.

There is no uniformity in the number of parasites in the blood; sometimes they are fairly abundant, one or two in each field of the microscope; at other times, and in the same patient, it may be difficult or impossible, even after prolonged search, to find a single specimen; in some instances they tend to recur cyclically at intervals of a week or more. On the whole, although with exceptions, the parasites are most abundant in the blood during the febrile attacks. Apparently the blood is not their only or their principal habitat. They are usually found easily in enlarged lymphatic glands, and have been seen also in the cerebro-spinal fluid, serous cavities, and in the substance of the solid organs, including the brain, where they are distributed throughout the tissues outside the blood-vessels.

The parasite may be cultured on N.N.N., or better still the Razgha-Reichenow medium. Reichenow (1940) produced a culture in which 70 per cent. had lost their blepharoplast after treatment with tryptoflavin, but all the survivors



Glossina brevipalpis Newstead. ♀ × 4½ (From Austen)



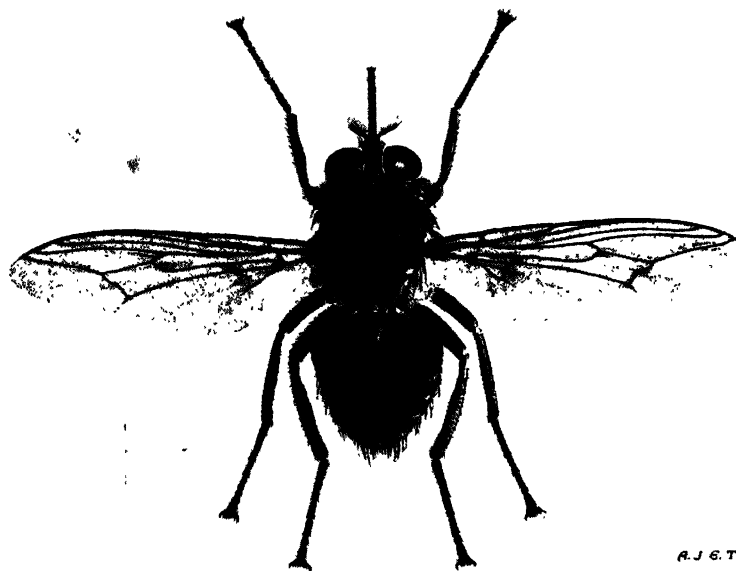
A. J. C. T. R. Z. W.

Glossina tachinoides Westwood. ♀ × 6 (From Austen)

TSETSE-FLIES

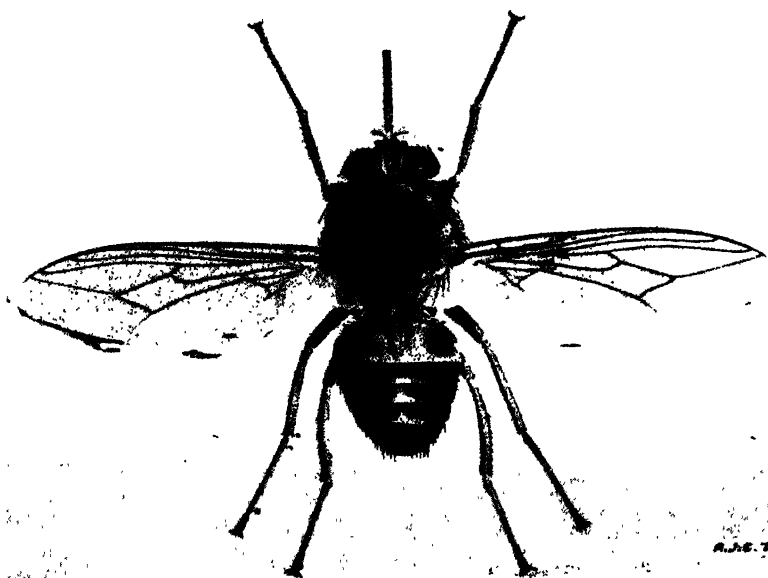
(By permission of the British Museum (Natural History))

PLATE IV



A.J.G. TERZI

Glossina palpalis Robineau-Desvoidy ♀ × 6 (From Austen)



A.J.G. TERZI

Glossina morsitans Westwood. ♀ × 6 (From Austen)

TSETSE-FLIES

(By permission of the British Museum (Natural History))

retained this structure suggesting that it may be necessary for cyclical transmission. The trypanosomes are maintained in culture at a relatively low temperature for several months, but development does not proceed beyond a stage similar to that in the proventriculus of the tsetse when they are not infective to animals. Developing hens eggs have been used as a medium with some success. It can usually be inoculated into most mammals, including all the ordinary domestic and laboratory animals, and is especially pathogenic for the rat, but shows considerable variations in virulence. Monkeys, especially *Erythrocebus patas*, and dogs are susceptible, while amphibia and reptiles are immune. Inoculation of susceptible animals may be used to demonstrate the parasites when they occur in very scanty numbers in the peripheral blood, and is sometimes successful in those rare cases where they cannot be found after careful microscopical examination.

As shown by Laveran and others, these trypanosomes undergo agglomeration, both in blood and in artificial cultures, when exposed to unfavourable biological conditions.

How long a trypanosome infection may persist in the human body has not been definitely determined, but there is direct evidence that it may continue for many years. From what we know of the incubation period of sleeping-sickness, it is not improbable that this period may extend to seven years or longer.

Transmission.—*T. gambiense* is not usually transmitted hereditarily in human beings, although the organisms have been found in the placental blood of infected rats, as well as in the livers of their embryos, but as in malaria and kala-azar, intra-uterine congenital transmission has been recorded in Germany in a European child born in Hamburg (Mühlens) and once by Capponi (1958) in the French Cameroons.

In the French Congo, Darré and his colleagues recognized congenital trypanosomiasis and demonstrated trypanosomes in the cerebro-spinal fluid of a child born of an infected mother. David and Pape (1942) described two in the French Cameroons where transplacental transmission was established, trypanosomes being found in the blood of the infants as well as in that from the umbilical cord.

Rôle of the tsetse fly as transmitting agent.—There is no evidence that biting flies other than the tsetse are concerned in the spread of human trypanosomiasis, but there are apparently two methods by which

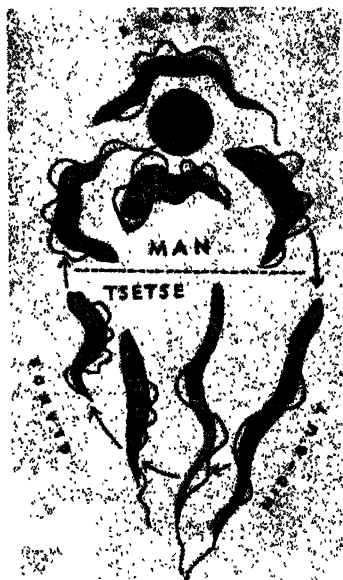


Fig. 13.—Life cycle of *Trypanosoma gambiense* and *T. rhodesiense*. (After C. A. Hoare.)

Trypanosomes in human blood, (Long slender form; Intermediate form; Short stumpy form; Stumpy form with posterior nucleolus).

Stages in the tsetse fly (trypanosome forms, in stomach, and in proventriculus; Crithidia, and Metacyclic trypanosomes in salivary glands).

Red blood-corpuscle drawn out of cell.

this fly is able to transmit trypanosomes: (1) cyclical, and (2) mechanical.

(1) *Cyclical transmission*.—As originally demonstrated by F. K. Kleine in 1909, *T. gambiense* undergoes an endogenous cycle of development in the circulating blood of the vertebrate. Certain short forms are regarded as the adult or metacyclic type, and they alone are responsible for carrying on the exogenous cycle. When ingested by the fly trypanosomes first multiply in the mid-gut; if the contents of the intestine at this stage are injected into the susceptible animal, they do not convey infection. After a cycle of development, lasting 12–20 days, the infective forms of trypanosomes congregate in the salivary glands. An important part is played by the peritrophic membrane lining the gut of the fly. (For further details, see p. 906.)

Cyclical transmission is influenced by the numbers of trypanosomes in the blood, by the host and by the blood plasma; it is diminished in chronic trypanosomiasis, in drug resistance and in exalted virulence of *T. gambiense*.

There is no doubt now that transmission ordinarily occurs through the bite of infected flies, trypanosomes passing through the salivary duct as do the sporozoites of the malaria parasite. The adaptation of *T. gambiense* to *G. palpalis* is remarkably specific. In Western Nigeria and in certain districts of the Gold Coast, however, *Glossina tachinoides* is naturally infected and is mainly responsible for epidemics of sleeping-sickness in those countries. There is no evidence that the tsetse can transmit the trypanosome to its offspring.

(2) *Mechanical transmission*.—Duke, in Uganda, suggested on epidemiological grounds that mechanical transmission by glossina of a virulent strain of *T. gambiense* from man to man might be responsible for some epidemics.

Reservoir-hosts.—In the plateau province, Northern Nigeria, Taylor found that, in the absence of game and suitable aquatic reptiles, which form normal buffers, the fly feeds for the most part on man. Shade, which is only found near villages, is also important. These two factors combine to bring man and fly into close contact, and the rate of trypanosome infection of the fly is correspondingly high. In Uganda the same conditions obtain.

It was formerly thought that wild game might act as reservoirs for *T. gambiense*, especially by Duke, who postulated that marsh-haunting antelopes, especially the situtunga, or Speke's antelope (*Tragelaphus spekei*) did so on the islands of the Victoria Nyanza, but this view is not now generally accepted. It has, however, been shown that eleven common species of antelope (bushbuck, reedbuck and waterbuck, etc.) can be inoculated with *T. gambiense*, but this does not prove that this is a common occurrence in nature, as in the case of *T. rhodesiense* in the bushbuck, which has recently been shown by Heisch and colleagues in Uganda to be the main reservoir of this trypanosome and therefore a danger to man.

In the arid districts of West Africa the flies are restricted to the more humid environment of wooded streams and cannot range far afield. They tend to haunt sites where women gather to draw water and wash clothes,

or where flocks are watered. The same group of flies thus tends to bite many human beings in succession, readily become infected and readily transmit trypanosomiasis. In the far more humid rain forest regions flies range widely and the chances of any one fly feeding on a single human, let alone a succession, are remote. It is thus in the regions with strictly seasonal rains followed by long, dry periods, that human trypanosomiasis flourishes.

Domestic stock must be now considered as probably the main reservoir of infection for man, since *T. gambiense* has been found by various observers in oxen, goats and sheep. Van Hoof has stated that in the Belgian Congo domestic pigs form ideal reservoir-hosts, but show no obvious ill effects themselves; further that the strain remained infective to man after 10 transmissions through those animals during the period of one year. Dogs have also been found infected.

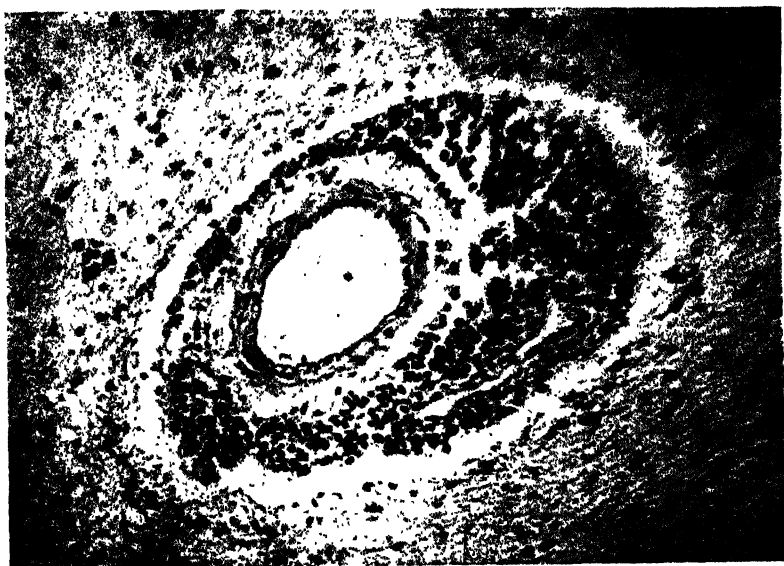


Fig. 14.—Perivascular cuffing in the cerebral cortex, due to trypanosomiasis.)
× 150. (Dr. A. C. Stevenson)

Pathology.—The chief lesions are in the lymphatic glands of the neck, submaxillary region and mesentery and in the central nervous system.

Central nervous system.—Typical pathological lesions are seen only when pathogenic trypanosomes have invaded the central nervous system. No gross lesions of the nerve centres are present, but there is progressive chronic leptomeningitis, especially in the Virchow-Robin space (where the pia sheaths the blood-vessels and the fluid acts as lymph). and also on the vertex (Dürk's nodes).

The dura may be adherent to the skull and to the arachnoid. The brain itself is congested and oedematous, the surface smooth, with convolutions flattened by increased pressure. The consistency of the brain tissue is unaltered, except for softening around any hæmorrhages that may occur. The ventricles are distended with fluid. In all cases there is perivascular lymphatic tissue (perivascular cuff) throughout the brain tissue and meninges, varying in amount and in different anatomical regions (Fig. 14). The invading cells are glia cells, lymphocytes, the morula (Mott) and Marshalko cells. The two latter types are degenerative plasmocytes. Morula cells stain deeply, with unilateral oval nucleus

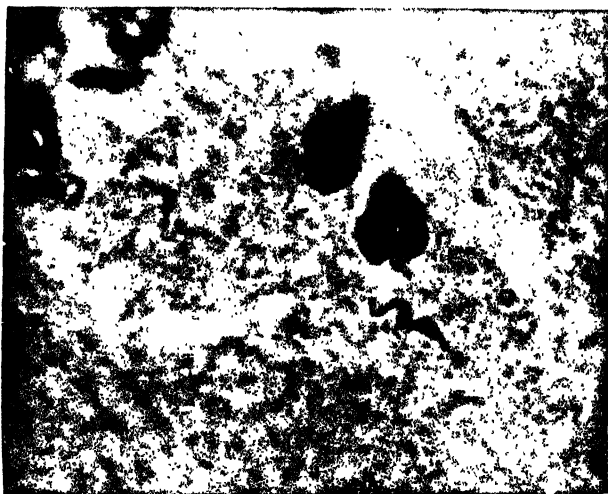


Fig. 15.—Photomicrograph of frontal lobe of brain in sleeping-sickness, showing trypanosomes in grey matter. (Dr. A. C. Stevenson, "*Trans. Roy. Soc. Trop. Med. and Hyg.*")

and vacuolated protoplasm. Marshalko cells are large plasma cells with a blue polar zone round the nucleus, with surrounding halo and acidophilic protoplasm.

As originally demonstrated by Wolbach in experimental animals and by Stevenson in man, in advanced cases, lesions in lymphatic glands and in brain are caused by invasion of the solid tissues by trypanosomes which have migrated from the bloodstream. In the brain they have been found mainly in the frontal lobe, pons and medulla, aggregated together in masses or nests without definite relation to blood-vessels (Fig. 15). Myelin lesions of the brain have been described by Van Bogaert (1936). The organisms also invade the cerebro-spinal fluid; they enter the canal from the choroidal plexus where they congregate, as Peruzzi has shown, in active stages of division. Optic atrophy due to trypanosomiasis has been recorded.

The spinal canal may even be blocked by cell proliferation. The cerebro-spinal fluid in early cases is under increased pressure (80–100

cm. of water); the total proteins being very much increased, to 1 grm. per litre (normal 0.2 grm.).

The cells are increased to 15 to 500 or more per c.mm. (normal 2-3) and comprise lymphocytes, mononuclears, morula cells, eosinophiles and trypanosomes.

Kidneys.—There is glomerular nephritis, leading to fibrosis, also a generalized proliferation of the reticulo-endothelium in the capillaries.

Heart.—Ecchymoses and even large hæmorrhages in the epi- and endocardium have been observed. Peruzzi has shown (in the pathology of experimental trypanosomiasis in monkeys) that severe myocarditis is frequently present and is due to masses of trypanosomes within the muscle cells.

Liver.—There is spoiling of parenchyma cells, probably from toxic absorption, associated with depletion of the blood sugar. A specific central lobular necrosis has been demonstrated in experimentally infected monkeys.

Lungs.—These are characterized by intravascular proliferation of the reticulo-endothelium, which may block the capillaries with fibrosis, and collapse of the alveoli.

Bone marrow.—The fat is reduced and the whole tissue may be gelatinous and homogeneous.

Skin.—Localized œdema, due to collections of lymphocytes, is observed in the eyelids, perineum and skin of the back.

The *spleen* is slightly enlarged. The Malpighian bodies are few and inconspicuous. There is a general proliferation of the reticulo-endothelium, congestion at the periphery of the splenic sinuses, often focal necrosis with endothelial macrophages and ingested red blood corpuscles. Giant cells have been observed.

Lymphatic tissue shows general hyperplasia. The glands are enlarged, soft and fusiform, with great proliferation of the lymphocytes. At first there is increase of large mononuclear cells, lymphocytes and later fibroblasts. They are very vascular, with small hæmorrhages containing trypanosomes (which can therefore be easily demonstrated by gland puncture).

The *blood* shows definite anæmia due to toxæmia and erythrophagocytosis. The hæmoglobin is reduced and colour index below normal. There is usually auto-agglutination of red cells with rouleaux formation (cold agglutinins). The alkali reserve is diminished and blood sugar low.

Symptoms.—The *incubation period* of the glossina-conveyed disease and that resulting from direct artificial inoculation seem to be about the same, from two to three weeks in dogs, horses and monkeys. From experience of infected Europeans, in whom the dates can be controlled, it appears to be about fourteen days. The bite of an infected glossina is followed, in a proportion of cases, by local irritation of greater or lesser severity. This has been called the "trypanosome chancre" and is described as a red nodule surrounded by a white waxen zone. Godfrey and Fairbairn (1957) have demonstrated the development of metacyclic trypanosomes in the "chancre" and think that the blood-stream is invaded from this focus some days after the bite. It subsides in a few days, to be followed, sooner or later, by fever, which may last a week or longer, and may be accompanied, in Europeans at all events, by a

peculiar type of erythema and a certain amount of serous connective tissue infiltration (Plate VII, Fig. 1). The trypanosomes appear in the peripheral blood about twenty-one days after the infecting bite. A form of hyperæsthesia, known as "Kerandel's sign," is usual, though not invariable; when the patient strikes any hard object he suffers discomfort amounting to actual pain after a slight delay. In time the fever subsides



Fig. 16.—Enlargement of cervical lymph-glands in trypanosomiasis (Winterbottom's sign). (*Dr. F. K. Kleine.*)

more or less completely, to recur at irregular intervals of days or weeks. It is sometimes mild, sometimes severe, and occasionally hyperpyrexial (106.6° F.), the evening temperature being always the highest. It may last for weeks and the apyrexial period may be equally prolonged, or it may be continuous. The fever and all other clinical manifestations of trypanosomiasis are irregular in intensity and duration. In time the patients become debilitated, anæmic and feeble, both intellectually and physically. The spleen is usually enlarged. Severe temporal headache

is very often present. The heart's action is generally rapid and easily excited and persistent tachycardia affords an excellent index to persistent infection. The cervical glands and those of other parts of the body enlarge and may become tender. Only one gland may be visibly involved, or there may be polyadenitis, including the abdominal group. The implicated glands may be very prominent, or not easily felt, but are usually most conspicuous in the posterior triangle of the neck (Winterbottom's sign) (Fig. 16). In the early stage of the infection they are soft, later indurated ; sometimes they are painless, sometimes distinctly painful and tender,

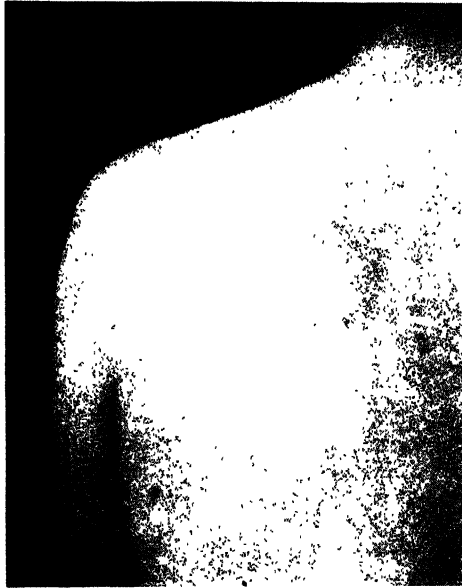


Fig. 17.—Trypanosome circinate rash. (Cooke, Gregg & Manson-Bahr.)

rarely suppurating. This condition of irregular fever, of debility, of polyadenitis, of slight anæmia, may go on for months, or even, in some instances, for years. At this stage there is usually insomnia and lack of concentration.

A proportion of cases may then terminate. Since this disease undergoes at various stages periods of quiescence, which may be very prolonged, it would be rash to call any instance of apparent recovery a radical cure. But experiments and observations by Laveran and others in other forms of trypanosome infection, as well as some cases in Europeans which have come under the Editor's notice, justify the belief that occasionally the parasite does die out spontaneously.

In a given area and in a given population there is a tendency for the virulence of the local trypanosome to decrease with lapse of time. Thus, the trypanosome of the Gold Coast and Southern Nigeria, where sleeping-

sickness presumably has long been endemic, is less virulent and much more amenable to treatment than that of Uganda, where it is of recent introduction.

Remarkable features of human as well as of animal trypanosomiasis are skin affections and local cedemas. In many of the lower animals infected by their special trypanosomes, papular and pustular eruptions are common, in addition to fever and physical lethargy; and in man, especially in negroes, an exceedingly itchy papular eruption is frequent. In the European, and possibly in the negro—but in the latter, less evident on account of his colour—extensive skin areas are affected with a fugitive, patchy, frequently annular erythema (Fig. 17 and Plate VII, facing p. 289), usually most evident on the chest and back, but also very often on the face, legs, and elsewhere. This erythema seems to occur most frequently and most distinctly in the earlier stages of the infection. Some of the patches may be six inches or even a foot in diameter, their margins fading off insensibly into the surrounding normal skin. It usually takes the form of large rings, occasionally complete, more frequently interrupted and irregular. Sometimes it is confined to annular rings on the shoulders (Fig. 17). Erythema nodosum sometimes occurs also. Pressure or any irritation of the skin gives rise at once to transient congestion from vasomotor paralysis of the skin capillaries. The rash can be brought out by heat, and especially by hot baths. Xeroderma and pruritus are often present in the terminal stages.

In some of the lower animals a usual feature is cedema of certain parts of the body, especially of the eyelids, the sheath of the penis, the under-surface of the abdomen, and the neck. Similar, though less extensive, cedemas occur in man, in whom they are most apparent in the face and about the site of the erythema. In many instances there is a general fullness of the features which, with concomitant flushing, is apt to convey a false impression of sound health.

Neuralgic pains, cramps, formication, and paræsthesiæ of different kinds are not uncommon. Painful local inflammatory swellings, which after a time subside without suppuration, have been seen in some cases; periostitis of tibiæ more rarely. Toxic iridocyclitis and choroiditis and deep cedema of the lower eyelid are sometimes met. The eye symptoms are not so evident in man as in the lower animals, interstitial keratitis in infected dogs being comparatively frequent.

In most cases the spleen is enlarged, sometimes enormously, fluctuating with the fever, in the absence of concomitant malaria which, however, is a not infrequent complication. The liver may be similarly affected.

Although trypanosome infection is not, as a rule, transmitted to the fœtus, the abortion-rate is increased from the normal 7 per cent. in Congo natives to 81.7 per cent., and the infant mortality-rate from 29 per cent. to 50 per cent. Trypanosomiasis in infants is extremely rare, though Kellersberger has recorded infection in one three weeks old.

Death from intercurrent disease, from rapidly developing cerebral implication causing convulsions, status epilepticus or coma may supervene at any stage of trypanosomiasis. Usually the case gradually drifts into the stage known as "sleeping-sickness." It is usually believed that the

development of the sleeping-sickness stage in trypanosomiasis concurs with and depends on the entry of the parasite into the cerebro-spinal canal.

Sleeping-sickness stage (cerebral trypanosomiasis).—The terminal stage of trypanosome infection sometimes exhibits acute features, and sometimes is exceedingly chronic. While an interval of several years, possibly eight, may elapse from the commencement of the infection to the development of this terminal stage (Rodhain), in the majority of cases the progress is much more rapid. The characteristic terminal symptoms depend on implication of the nervous system, either by the parasite itself or by its toxins.

The average duration of this stage in the African is from four to eight months, not infrequently less ; very chronic cases with a course of more



Fig. 18.—Cerebral trypanosomiasis. Appearance of patient in last stages of the disease. (Dr. F. K. Kleine.)

than a year are rare. Some observers refer to cases running on for three years or even longer, with occasional temporary ameliorations.

Generally, the first indications of the oncoming of sleeping-sickness are merely an accentuation of the debility and languor usually associated with trypanosome infection. There is disinclination to exertion ; slow, shuffling gait ; morose, mask-like vacant expression ; relaxation of features ; hanging of the lower lip ; puffiness and drooping of the eyelids ; tendency to lapse into sleep or a condition simulating sleep, somnolence or "near coma" during the day-time contrasting with restlessness at night ; slowness in answering questions ; shirking of the day's task. Dull headache is generally present. He will walk, if forced to do so, with unsteady and swaying gait. Later, there may be fibrillary twitching of muscles, especially of the tongue, and tremor of the hands, more rarely of the legs, indicating involvement of the motor centres. His speech is difficult to follow, becoming indistinct and staccato. By this time the patient has taken to bed, or he lies about in a corner of his hut, indifferent to everything

going on around him, but still able to speak and take food if brought to him. He never spontaneously engages in conversation, or even asks for food. As torpor deepens he forgets even to chew his food, falling asleep perhaps in the act of conveying it to his mouth, or with the half-masticated bolus still in his cheek. Nevertheless, such food as he can be persuaded to take is digested and assimilated. Consequently, if he is properly nursed, there may be no general wasting. So far the striking features are the mental and personal changes with a paucity of neurological signs. As time goes on, he begins to lose flesh, tremor of hands and tongue becomes more marked, and convulsive or choreic movements may occur in the limbs or in limited muscular areas. (Fig. 18.) Sometimes these convulsions are followed by local temporary paralysis. Sometimes, too, rigidity of the cervical muscles and retraction of the head occur. There is usually an intolerable pruritus of the skin; bedsores tend to form; the lips become swollen, and the saliva dribbles from the mouth. Gradually the lethargy deepens; the body wastes; the bedsores extend; the sphincters relax; and finally the patient dies comatose, or sinks from slowly advancing asthenia. Possibly he succumbs to convulsions, hyperpyrexia, pneumonia, dysentery or other intercurrent condition. Clinically, then, sleeping sickness reproduces the picture of a true encephalitis.

The manifestations described are subject to considerable variations. Thus, mania is not uncommon; delusions may present themselves, or psychical and physical symptoms not unlike those of general paralysis of the insane are developed. In the European, death is frequently due to convulsions, probably from the presence of the trypanosomes in the brain. Deep hyperæsthesia of the muscles is also quite common. The habits usually become bestial and he becomes a drooling, dribbling and drowsy idiot. Gelfand has drawn attention to transitory neurological signs, such as ptosis and ophthalmoplegia and transitory paralyses, such as facial palsy, meningitic symptoms, accompanied by papilloedema and extensor plantar responses.

Trypanosomiasis in natives.—Three categories in Nigeria are recognized:—

- (1) Mild, with few symptoms, when equilibrium has been established between patient and parasite.
- (2) Involvement of the central nervous system—the commonest form.
- (3) Acute, leading to death before the central nervous system symptoms develop, toxæmia being the salient feature. Rainant (1957) finds that in the majority of cases in Africans there are periods which are predominantly depressive or exultative in type, alternating with periods of progressive mental deterioration tending to a paranoid state.

Elsewhere the same three types are found, but the acute form predominates, especially in Tanganyika, where *T. rhodesiense* is the common parasite.

Mortality.—Although spontaneous recovery may take place in the early stages of trypanosomiasis, it is believed that when the disease has

arrived at the stage of sleeping-sickness, in the absence of treatment, death is inevitable. Corr  has told how native villages in Senegambia have been depopulated. What has occurred on the Congo, in Angola, and in Uganda, bears out this estimate of the gravity of the disease in epidemic form. Many islands in the Victoria Nyanza have been completely depopulated. The population of the implicated districts of Uganda, originally about 300,000, was reduced in six years to 100,000 by sleeping-sickness.

Immunity.—Man is immune to infection with the commoner trypanosomes of big game, *T. congolense* and *T. vivax*, and certain mammals are immune to trypanosomes which are pathogenic to others. Thus, *T. vivax* is pathogenic to horses and cattle, whilst rabbits, guinea-pigs, and mice are refractory. Although there is no direct evidence that man becomes immune after exposure to infection with *T. gambiense*, yet there is no doubt that when the disease has lasted any length of time in a district, as in Southern Nigeria, the inhabitants exhibit a degree of resistance not seen in districts more recently invaded.

The non-immune European generally suffers in a more acute form than does the Central African native under similar conditions. Russell and others who have studied the phenomena of immunity in man believe that the course of an infection with a pathogenic trypanosome depends upon the capacity of that organism to vary in a serological sense so often that it defeats possible variations in the host's defence.

Diagnosis.—Chronic irregular fever, more especially if associated with enlarged cervical glands and, in the European, erythema multiforme, in a patient who has resided in tropical Africa at any time during the previous seven years, but especially recently, suggests a tentative diagnosis of trypanosomiasis and detailed examination with this possibility in view. Diseases with which trypanosomiasis might be confounded are malaria, kala-azar, pellagra, syphilis, leprosy, lymphadenoma (Pel-Ebstein disease), and, in its later stages, beriberi.

The diagnosis of trypanosomiasis is made absolute by blood examination, but the serum-formalin reaction (*see* p. 150) is usually positive in well-established cases and therefore may serve as a rough guide for differentiation from other African fevers on a large scale (Hope-Gill, Morrison, Dye and Cookson). Sic  and his collaborators have shown that there is a considerable diminution in the total serum proteins, and the loss is mainly due to decrease in serum albumin. The ratio of serum albumin to globulin is always less than it is in normal persons. Davis, Broom and Brown have worked out a specific immunity reaction in trypanosomiasis known as the "adhesion phenomenon." This reaction is characterized by adhesion of blood platelets and cells to the parasite when acted upon by immune plasma *in vitro*. For this purpose trypanosomes, immune serum, complement and human cells are incubated together; if the serum is homologous the red cells become firmly adherent to the trypanosomes. Standard concentrations of red cells and trypanosomes are necessary to obtain constant results. Agglomeration and trypanolysis may take place, even if the red cells are unsuitable as indicators. This reaction is said to be specific for different species of trypanosome, and the immune body exhibits a high degree of thermostability. The test can be used in recognizing species of animals which may act as reservoirs of *T. gambiense*, and of *T. rhodesiense* as well.

In an endemic area Saunders found that 91 per cent. of proved human cases gave some degree of adhesion in this test, whilst 75 per cent. of controls gave none.

Complement-fixation.—Van Goidsenhoven and Schoenaers (1954) have elaborated a quick and simple method for collecting and preserving trypanosomes for the preparation of antigen for this test. Evens and colleagues later have improved upon this by devising a technique for obtaining trypanosomes from rats by the injection of ephedrine. This test with an antigen prepared from *T. equiperdum* is highly specific for *T. gambiense* in man and which becomes negative after successful treatment.

Compared with other methods of diagnosis—gland puncture, search for parasites, CSF, cellular and protein content, Weichbrodt's globulin reaction—in relation to it, this test gives a 10 per cent. greater proportion of cases infected with *T. gambiense*.

Sedimentation rate.—The ESR is high in patients suffering from trypanosomiasis. For this purpose the Westergren is more sensitive than the Wintrobe method. Gall and colleagues (1957) found that a delay of five hours after withdrawal of blood has a negligible effect. Sedimentation readings should be taken at 10-minute intervals, but in practice 30 and 60-minute readings suffice. The median one-hour rate varies from 15–76 mm. In untreated cases it may be as high as 114 mm. Increase in ESR is closely associated with red-cell clumping which is evident. The term pseudoagglutination is the best term, because the plasma in these cases agglutinates red cells other than its own.

Microscopical diagnosis of trypanosomiasis is sometimes difficult. Anæmia, as well as a relative increase of large mononuclear leucocytes, usually occurs. A well-stained blood preparation exhibits, even to the naked eye, a remarkable clumping of the red corpuscles (autoagglutination). As a rule, the parasites in the peripheral circulation are few, many fields having to be hunted before one is discovered. Sometimes none can be found; rarely are they abundant, as in the acute forms of *T. rhodesiense*. The thick-drop method should always be employed and it is estimated that it takes 20 times as long to find them in thin as in *fresh wet-drop* preparations.

Blood centrifugation.—Take into a 10 ml. syringe 1 ml. of 6 per cent. sodium citrate in 0.9 saline. Fill the syringe with blood from a vein. Centrifuge for ten minutes on the low gear of the two-gear centrifuge. This brings the red cells down as a sediment, on the surface of which the leucocytes form a grey layer. Supernatant fluid is pipetted off into another tube. Examine the leucocyte layer and first sediment for trypanosomes. Re-spin supernatant in the high-speed gear for ten minutes and pipette off into a third tube. Examine the second sediment which occasionally reveals trypanosomes (in 16 per cent.). The third sediment similarly treated often has trypanosomes in 39 per cent. Sicé (1937) advised that the electric centrifuge should not exceed 3,000 r.p.m.

Greig and Gray, Dutton and Todd emphasized the value of *lymph-gland puncture* and examination of the aspirated lymph as the most certain method, particularly in the earlier stages of the disease, when the glands are soft before they have become sclerosed, and the trypanosomes abound

in the lymph. This method succeeds in 87.7 per cent. of cases. The procedure is as follows:

- (a) The gland is gripped between finger and thumb of the left hand and massaged.
- (b) A hypodermic needle (size 14) is pushed through the skin into the substance of the gland which is then squeezed further.
- (c) The needle is withdrawn and its contents gently blown out on to a slide by means of a hypodermic syringe filled with air.
- (d) A coverslip is applied and the unstained preparation is *immediately* examined beneath the $\frac{1}{8}$ " objective. Intensely active trypanosomes are easily recognized in a positive case. They can be subsequently fixed and stained.

Gland-puncture should always be reinforced by the examination of thick blood-films. The glands may be unilateral or bilateral; sometimes they reach the size of a pigeon's egg and every gradation may be shown. Although the superficial glands may be easy to palpate, deeper ones may be more difficult. Three procedures for palpation are necessary: deep palpation, superficial palpation, and palpation by passing the palmar surface of the hand over the neck. The glands should have the consistency of a ripe plum. Harding and Hawking (1945) found both gland and blood examination positive in 30-40 per cent.; gland puncture positive, blood-film negative in 50-60 per cent.; blood-film positive, gland puncture negative in 10 per cent.

Cerebro-spinal fluid, obtained by lumbar puncture and centrifuged, affords another (though not always a practicable) means of finding the parasite; according to Broden, parasites may be demonstrated in this manner in 4.5 per cent. of cases, but if the trypanosome is not found, suggestive information may be obtained from a lymphocyte-cell count of the fluid, as this may be increased to over 1,000 per c.mm. The globulin content of the fluid is also increased, but the colloidal gold curve is of the paretic type. With 4 ml. of fluid centrifuged trypanosomes are found in 0.15 per cent. of cases.

The diagnosis of trypanosomiasis is not justified on a cell count as low as 15 or 20. The limit should be about 30 cells. When present the morula cells of Mott are suggestive. The protein estimation appears to be open to the same objections as the cell count.

The importance of puncture of the cerebello-medullary space in the diagnosis was emphasized by Tajera. Suboccipital puncture through the occipito-atlantoid ligament into the *cisterna cerebello-medullaris* is simple and practically devoid of risk.

Hutchinson states that while the CSF protein content indicates the stage which the disease has reached, the CSF cell-count reflects the activity of the cerebral disease at any one time.

Sicé has proved that the earliest reaction resulting from meningeal lesions is cellular; at first it is slight and unaccompanied by clinical signs; usually it progresses slowly, and the intensity of the meningeal lesions is shown by the number and character of the cells. The presence of leucocytes indicates that the lesions are active and, probably, recent.

Plasma cells, dead cells and morula cells indicate older and more chronic lesions. Prognosis can be based upon the amount of albumin in the spinal fluid.

Animal inoculation is used if the parasite is not found by blood or lymph examination, 2-10 ml. of the blood being drawn from a vein and injected. Of the ordinary laboratory animals, the most susceptible, and therefore most reliable, are the guinea-pig, the rat, the dog, and *Macaca* and *Cercopithecus* monkeys. Such inoculations are of value as a test of recovery, as well as for diagnosis. The best animals on the Gold Coast are the green cercopithecus monkey and the pouched rat—*Cricetomys gambianus*. 10 ml. of citrated blood are used for monkey, cat or dog; 3-6 ml. for *Cricetomys* and 1 ml. for a small rat. Interval between inoculation and appearance of trypanosomes in the peripheral blood varies from 6-49 days. Relapse can be produced by intraperitoneal injection of olive oil.

Sternal puncture has recently been introduced as a reliable and ready method of diagnosis. Guibert and Boscq found *T. gambiense* in the bone marrow of 29 out of 30 untreated cases, whilst Lenhard, Jospin and Gallais claim that it is superior to any other method.

The trypanosome is easily stained by most dyes, those in use for malaria work giving the best results. A $\frac{1}{8}$ -in. objective suffices to find the parasite.

Differential diagnosis.—Kala-azar and trypanosomiasis, especially in their earlier stages, may be difficult to differentiate, but enlarged glands, local oedema and erythema multiforme in trypanosomiasis, and their absence in kala-azar, suffice for distinction. Blood or gland-lymph examination, or, if this be negative, hepatic or splenic puncture, should establish the diagnosis.

General paralysis of the insane, cerebral tumour, forms of meningitis, especially encephalitis lethargica (often inaptly termed "sleepy sickness"), have features in common with trypanosomiasis and must be considered. The serum of some cases of trypanosomiasis has been said to give a positive Wassermann reaction, but this may be due to a co-existing syphilitic infection.

TREATMENT

Especially in natives, preliminary treatment directed towards eliminating superimposed infections with ancylostomes or schistosomes is advisable, on account of damage to the liver-cells which renders toleration of arsenical drugs difficult.

1. *Antrypol* (see p. 867, Appendix) "Bayer 205," introduced in 1920, is valuable in eradicating trypanosomiasis, especially in the early stages.

In artificially injected animals it is non-toxic. The *dosis tolerata* is estimated at 160 times the *dosis therapeutica*, injected intramuscularly or intravenously, being lethal to *T. brucei*, *T. gambiense* and *T. rhodesiense* and moreover it exerts a prophylactic action.

The average dose for man is 10 ml. of 10 per cent. solution in distilled water intravenously. The total amount to effect cure is 10 grm., though trypanosomes usually disappear after 5 grm. The dose should be repeated at weekly intervals.

In early infections the best and most lasting results are usually obtained by larger initial doses, such as 1 grm. on the first, third, tenth and thirteenth days. Sometimes doses of 1.5 to 2 grm. are given. Although it is most active in destroying trypanosomes in the blood it is incapable of doing so after they have entered the brain.

The value of antrypol lies in its power of rendering the trypanosomes fit for phagocytosis by the reticulo-endothelial cells—a kind of opsonizing effect. This action greatly enhances the effect in the living animal and thus explains its efficacy *in vivo* rather than *in vitro*. There are also good reasons for believing that its delayed action is due to combination with plasma and tissue proteins, so that serum, cerebro-spinal fluid and urine continue to exhibit subsequent trypanocidal action when injected into trypanosome-infected mice. Intrathecal injections are not recommended.

Immediately after the injection of the drug both the physical condition and mental outlook of the patient are improved. The drug is harmless to man, except that it has a cumulative action and is a kidney irritant, so that, after three or four injections, the urine contains albumin and small yellow, granular casts. This is the result of excretion *via* the urinary tubules, and lasts about six weeks. In some susceptible individuals toxic dermatitis—a red, itching and papular rash—develops, usually after the third injection. According to Corson, a painful condition of the feet, apparently peripheral neuritis, has sometimes been observed. A rare but disagreeable sequel is exfoliative dermatitis.

2. *Tryparsamide*.—Tryparsamide should not contain less than 25.1 per cent. of arsenic. "Fournau 270" (Orsanine) is the French equivalent.

Tryparsamide, when injected, is quickly absorbed, either by the intramuscular or intravenous routes. The chemotherapeutic index—the ratio between the curative and maximum tolerated dose—is 1 : 2 ; for atoxyl it is 1 : 1.

Individual doses are large, varying from 1 to 4 grm. (the maximum is 60 mgm. per kg. body weight). The drug exerts a marked effect on symptoms, especially when the nervous system is involved. Its chief value lies in the ease with which it penetrates into the cerebro-spinal fluid, where it eliminates the trypanosomes. The great reduction in the lymphocytes in the cerebro-spinal fluid in cerebral trypanosomiasis is attributed to its high power of penetration. In average cases the initial dose should be 1 grm. in 10 ml. of distilled water, subsequently 2 grm. three times weekly. A total dosage of 24 grm. is necessary.

In chronic cases the dosage may have to be as high as 70–80 grm. for permanent cure, according to Van den Branden, but in mild infections he obtained 57 per cent. apparent cures with a total of 20–60 grm., but in a smaller percentage when trypanosomes were present in the cerebro-spinal fluid.

Chesterman concluded that, to be effective, solutions should not exceed 40 per cent. which is near saturation point. The water must not be alkaline which produces precipitation. Intramuscular injections are also efficacious, but this solution should not be stronger than 20 per cent.

Prolonged administration of maximum tolerated doses gives the best results. Children up to twelve years tolerate the drug well and may be given up to 20 mgm. per kg. body weight for 12 injections. If the drug is used in strengths of more than 20 per cent. by the intramuscular route induration or abscesses may result. Herxheimer reactions with acute mania have been recorded with excessive doses.

In *advanced* cases in adults the initial dose should be 20 mgm. per kg., on the fourth day 30 mgm. per kg., while on the eighth a course of 20 injections of 40 mgm. per kg. at four-day intervals should be commenced : after a three-months' interval a course of 10 injections should be repeated.

As evidence of *cure*, physical improvement and restoration of mental activity,

together with a normal cell-count and albumin content of the cerebro-spinal fluid for one year should be taken into account.

An excess of albumin and increase of cells is sometimes noted for a short period, but may be only temporary.

Arsenic resistance.—This subject has been much debated. Van Hoof states that it is often difficult to create this in the laboratory, whilst routine treatment does not inevitably increase it in the case of a relapse; but in mass treatment (as in the Belgian Congo), where this resistance is on the increase in an endemic area, it is rather because the routine treatment has eliminated a large number of non-resistant strains from the trypanosome reservoir.

Non-resistant strains are usually more easily transmitted through the tsetse.

Results.—In early cases an apparent cure is almost invariable, but tryparsan acts less satisfactorily after previous administration of atoxyl (or other arsenic). In advanced cases it is less certain, but in the absence of other debilitating disease and when degeneration of the central nervous system has not progressed far, and when the cerebro-spinal fluid does not contain too many cells, trypanamide gives gratifying results.

Optic neuritis.—Some are particularly sensitive to trypanamide and optic neuritis is apt to develop in patients previously treated with smaller quantities, and to whom a second course is given. Sometimes it occurs after comparatively small doses and the Editor has seen three where blindness ensued in doses ranging from 5–13 grm. Jamot reported that, out of 25,638, 233 developed ocular troubles; in 30 amblyopia and in 17 amaurosis, but Basten, in cerebral syphilis, in a larger series, has not experienced the same amount of ocular trouble.

Ridley (1943) classifies disturbances of vision into four stages:—

- (1) Metamorphopsia and a sensation of shimmering movement (objective).
- (2) Depression of vision, loss of peripheral field for even large objects, followed by decrease in central acuity. The appearance of the optic discs still remains normal.
- (3) After an interval of two weeks, pallor, unaccompanied by swelling and vascular abnormalities, appears in the optic discs and the victim becomes completely blind with very inactive & dilated pupils.
- (4) Stage of recovery, which may proceed for three to six months, in which there may be complete return of central acuity with some degree of improvement in the peripheral fields. The pallor of the discs remains unchanged and may even progress.

OTHER ARSENICALS

Melarsen oxide (disodium *p*-2:4-diamino-1:3:5-triazinyl-6-aminophenyl-arsenate), having an arsenic content of 20.2 per cent., was prepared by Friedheim and was tried out in West Africa. It was then produced by him in combination with BAL (or 2'-3'-dimercaptopropanol or dimercaprol) which renders it less poisonous and the compound is then known as *Melarsen B*, mel B, or arsobal. It sterilizes the blood and causes improvement in the cerebro-spinal fluid. Duggan and Hutchinson (1951) found mel B, in short courses of 8 injections at five-day intervals, at least as effective as trypanamide, but toxicity is greater, and melarsen must now be regarded as the premier drug in the treatment of trypanosomiasis (of late disease with neurological involvement).

Melarsen oxide/BAL (arsenobal) in 3.6 per cent. solution has achieved a reputation in the treatment of trypanosomiasis in Portuguese and French West Africa. It is claimed that early cases are cured by one dose of 4 mgm. per kg.; second

stage cases with up to 20 cells in the C.S.F. by three doses in weekly injections. Late cases are treated with three or four courses of the above regime. *Butarsen* (70A), an American product, is effective in early cases. The antimonial analogues—*Msb* and *Msb*₃—also produced by Friedheim, are said to be very active (Le Rouzic, 1949).

Sterckx (1953) in Usumburu, Congo, has reported on 109 cases of trypanamide-resistant cases treated with "Mel B" (arsobal). The immediate recovery rate appeared to be about 75 per cent., but the treatment must be carried out in hospital under control. It is of rare efficiency, and with care, does not lead to a greater number of accidents than do other trypanocides.

Melarsen (without BAL) has been reported upon on an extended scale by Butler, Duggan and Hutchinson (1957) under field conditions in N.E. Nigeria, in a series of 180 cases. In treatment courses with a dosage of 20 mgm. per kgm. the incidence of toxic effects was 2·8 per cent. It is considered that this should be regarded as the maximal dose. A course of 12 injections each at 5-day intervals is advocated to reduce the possibility of arsenic resistance. In early cases the cure rate is excellent, and in advanced cases melarsen gives better results than standard courses of treatment with trypanamide.

OTHER PREPARATIONS

Diamidino stilbene (stilbamidine) (see also p. 152). This was found to be active in experimental trypanosomiasis and was tried out in Nigeria and Gambia by Harding and Bowesman. Intravenous injections are apt to be followed by temporary symptoms, but it may also be injected intramuscularly. It banishes the trypanosomes, but is unsuited for cases with protein content in the cerebrospinal fluid above 0·05 per cent. The treatment takes about half the time necessary for trypanamide.

Pentamidine was tried out by Lawson and Gilbert (1943) in Uganda and Northern Rhodesia as well as by Saunders on the Gold Coast. It was given daily for 18 days intramuscularly in doses varying from 1·6 to 5·15 mgm. per kg. Those with cell counts in the cerebrospinal fluid less than 30 per cmm. were usually cured. By the intravenous route at least 2 mgm. per kg. should be given. Serious fall in blood pressure is avoided by injecting the drug very slowly. McComas and Martin (1944) recorded a fatality in an African after three injections, death being due to a Herxheimer reaction. Polyneuritis has also been recorded. McLetchie in Nigeria considered that it is equal to antrypol. Pentamidine isethionate (*lomidine*) is the salt used: 100 mg. on the first day, then 200 mg. daily to the seventh day. Hutchinson now considers Pentamidine the drug of choice in early cases without CSF changes and advocates seven daily intramuscular injections, each dose being calculated on a basis of 2–3 mgm./kgm. body-weight. In later cases with CNS involvement the course should be supplemented with trypanamide 2 gm. intravenously every fifth day for 8–12 doses.

Synergic or combined treatment.—Striking recoveries have been secured by combining antrypol and trypanamide therapy—which is borne out by the experimental work of Yorke indicating that pathogenic trypanosomes may become drug-fast, and that resistance to antrypol is brought about very slowly.

Harding (1946) in Sierra Leone has compared the following types of treatment :

(1) Antrypol—5 doses of 1 grm. at 5-day intervals in cases with normal cerebrospinal fluid.

(2) Trypanamide, 6–10 doses of 2 gm. at 5-day intervals (9–10 doses).

(3) Antrypol—3 doses of 1 grm., followed by trypanamide, 3–5 doses of 2 grm.—all at five-day intervals.

(4) Two combinations of antrypol and trypanamide, 3–7 doses of 2 grm. at five-day intervals :—

(a) Antrypol—3 doses of 1 grm. followed by tryparsamide, 3–7 doses of 2 grm. An interval of five or seven weeks separated the first and second courses; the remainder were given at five-day intervals.

(b) Antrypol—2 doses of 1 grm., followed by tryparsamide, 4–6 doses of 2 grm. at five-day intervals.

The cerebro-spinal picture was taken as the only reliable index of cure. In mass treatment in Nigeria the total antrypol is 3.2 grm. followed by tryparsamide 10 grm. in 9 injections at intervals of 5 days. The first injection of 0.2 grm. antrypol is a test for idiosyncrasy.

Transmission of drug-resistance through the tsetse.—Yorke and his colleagues discovered an important fact—that strains of trypanosomes possessing a high degree of resistance are transmissible by the tsetse (*transmission of an acquired character*) and that this remains unimpaired after two successive passages through the fly; but Van Hoof on the Congo has found that the non-resistant strains are usually more easily transmitted. Resistant strains which can be transmitted with great difficulty are derived from chronic well-treated cases. These more resistant strains usually constitute the minority.

Prophylaxis.—Prophylactic measures are based principally on the habits of *Glossina palpalis*, *G. tachinoides* and other species which may transmit *T. gambiense*. The measures employed are so similar to those in use against *T. rhodesiense* and so interwoven that they must be considered together in the section on the bionomics of glossina (*see p. 1067*). Other control measures consist of fly traps, barriers, clearings, block systems and the employment of DDT to destroy adult flies (*see p. 861*). Complete scientific prophylaxis can be established with certainty, only after we are in possession of full knowledge of the habits of the tsetse and the reasons for their restriction to limited and capriciously distributed areas, and also of the vertebrate hosts of the trypanosomes.

Destruction of big game.—The abolition of big game has been undertaken on an extensive scale. Unfortunately it appears to be true that where antelopes and buffaloes exist in large numbers there the tse-tse is to be found in abundance. In areas which have been cleared of these animals the destruction of the tse-tse appears to be a practicable proposition. An experiment in this direction was undertaken in a large block, comprising 700 sq. miles, in the vicinity of Shinyanga, Tanganyika. Originally large numbers of *G. morsitans*, *G. swynnertoni* and *G. pallidipes* were present. Measures commenced in July, 1945, and since that date 8,500 head of animals have been destroyed. The larger big game have been eliminated and a great reduction of impala and reedbuck has taken place. As a result *G. swynnertoni* has now disappeared and a great reduction of *G. pallidipes* has been recorded.

Repellents.—Little information is obtainable on this subject, but Holden and Findlay (1944) found that an anti-mosquito cream (containing pyrethrum) has a repellent action chiefly against *G. palpalis* for six hours, when applied to the skin, but this action is apt to be destroyed by heavy sweating with exposure to strong sunlight. The most popular at present is *Dimeepol* which contains dimethyl phthalate and ethylhexandiol in non-greasy basis and can be dissolved in a small amount of liquid paraffin for use in fly country.

Chemoprophylaxis.—A prophylactic injection of antrypol does not prevent actual infection, though it does mitigate the pathogenicity of the infecting trypanosomes. Fourché, on the Congo, concluded that intravenous injection of 1 grm. in adults, and 0.3 to 0.75 grm. in adolescents is of definite prophylactic value for seven months, but McLetchie in Nigeria has reduced this figure to six weeks. Van den Branden injected all the inhabitants of a village in the Belgian Congo with the following doses: adults 1 grm., adolescents 0.5 grm. and children

0.25 grm., infants 0.18 grm—each receiving two injections. Duke's statistics in Uganda seemed to indicate that prophylactic action may last three weeks. Olovitch (1927) reported favourably on mass injection (or moranylisation) of the native population of the Belgian Congo.

In Sierra Leone Harding and Hutchinson (1950) think that in that country a stage has been reached when it is justifiable to undertake mass prophylaxis with pentamidine. A trial of pentamidine in French West Africa was successful in protecting over 1,000 persons for six months, whereas 19 infected cases were found in 902 controls (Brun-Buisson).

Propamidine has the same action as pentamidine. An experiment in drug prophylaxis with propamidine was carried out in the Belgian Congo and has been described by Fain and de Mulder (1949) who have demonstrated that two intramuscular injections of 300 mgm. for men (less for women and children), at an interval of six months, served to protect for a period of two years, though examination of the cerebrospinal fluid showed that a cryptic infection still persisted. Controls, however, showed many more infections. They assert that even a single dose has considerable protective value.

The latest results of Van Hoof and his colleagues in the Congo were as follows: they find that one dose of pentamidine (2-3 mgm. per kilo body weight) injected intramuscularly can protect for six months. This appeared to be optimistic. The average weight of the Congo native is 40 kg. and, by raising the injection to 5 mgm. per kg. for protective action, good results have been obtained. It should be noted that the isethionate salt is used; not the hydrochloride. Both propamidine and pentamidine isethionate should be given in 1.25 per cent. solution intramuscularly. McLetchie in Nigeria considers 100 mg. pentamidine isethionate intravenously constitutes the best and most enduring method of protection.

Other prophylactic measures.—Brilliant results have attended the efforts of the Portuguese to combat sleeping-sickness in the island of Príncipe, where the annual mortality from the disease amounted to 83 per thousand of the population, and the local industry (cocoa) was threatened with extinction. Besides jungle-clearing, drainage, blood examinations, segregation of the infected, and destruction of possible animal reservoirs of the trypanosome, natives, dressed in white and carrying on their backs a dark cloth smeared with birdlime, were sent into the jungle, and every night the flies caught were removed and counted. In three years 470,000 glossinæ were caught. As a consequence of this combination of sanitary measures the fly and the sleeping-sickness were exterminated. Of course, it was only the complete isolation and the limited size of the island that made such a result possible.

The Anchau experiment in Nigeria provided a model example of the method of clearing an area of tsetse flies as well as of benefiting the population generally and of raising their level of culture. Anchau is now a tsetse-free corridor, linking two of the railway lines that diverge from Zaria, and is some 65 miles long, over 600 square miles in extent and with a population of 50,000. The combination of partial and barrier clearings has proved effective. The work on this scheme entailed preparation of maps, surveys, construction of roads, clearing 110 miles of stream, sinking of wells, study of local soils and vegetation, agricultural experiments and monthly fly surveys. The land allowance is 4.3 acres per person. Areas are reserved for plantation of wood and grazing.

Removal of infected populations.—Trypanosomiasis has interfered with the development of one-quarter of the African continent. In Uganda by 1900 it was estimated to have exterminated two-thirds of the native population. To preserve the hitherto uninfected from trypanosome infection, the Government transported the entire population of the Sesse Islands and neighbouring shore of Victoria Nyanza to fly-free areas in the interior. It was hoped that, the human source of trypanosome supply being thus denied them, the tsetse flies would cease to be infective.

Unfortunately, this hope has been disappointed. Three years after the depopulation of the districts involved, Bruce ascertained that local flies could still convey the disease to laboratory animals. Manifestly, *T. gambiense* can flourish under natural conditions in vertebrates other than man. The reservoir host in this instance was thought to be the situtunga antelope.

Prognosis—The state of the C.S.F. is most important. Increase of total protein is of more significance than cell increases. If the C.S.F. is abnormal after treatment the cell count is the more delicate indicating cure or failure. The Sicard Canteloube method of estimating total protein (normal 22 mg. per cent.) should be used. The blood sedimentation rate is also useful.

[For a detailed description of tsetse flies (Plates IV, V) and preventive measures at present in use, *see* pp. 1070–1073.]

RHODESIENSE SLEEPING-SICKNESS

The trypanosome found in cases of human sleeping-sickness originating in Rhodesia was at first considered to have certain peculiarities when inoculated into the rat. This fact, together with the greater



Fig. 19.—Male Bushbuck (*Tragelaphus scriptus*), Kenya.
(A. W. Guggisberg, Nairobi.)

virulence of the disease both in man and in laboratory animals, and the greater resistance to arsenical treatment, led Stephens and Fantham to separate it as a distinct species under the name of *T. rhodesiense*, in 1910. Later, it was proved that it is transmitted by *Glossina morsitans* (Kingham and Yorke), not by *G. palpalis*, and that *G. swynnertoni* is also an efficient intermediary.

Kleine regarded *T. rhodesiense* as the form taken by *T. gambiense* when introduced into a new area and transmitted by tsetse flies of the *morsitans* group, and as distinct from *T. brucei*. The question has now been settled by MacMahon, Heisch and C. Manson-Bahr in Kenya who have transmitted *T. rhodesiense* from the bushbuck (*Tragelaphus scriptus*) to a human volunteer. The infection was first passed through the rat.

Yorke and his collaborators pointed out that the selective cytolytic action of normal serum on trypanosomes and the resistance of *T. gambiense*, in contradistinction to *T. rhodesiense*, may be the true explanation. By this test, *T. rhodesiense* and *T. brucei* appear to be identical, but the serum resistance of *T. rhodesiense* is not a fixed or stable character, but one which is readily acquired and quickly lost. The fact is that there are no constant differential characters in these two human trypanosomes. The *rhodesiense* type is undoubtedly more virulent than *gambiense*, as the latter has become habituated to man by long residence in his body, whilst the former is a more recent acquisition associated with *G. morsitans*, and usually with big game, especially antelopes.

The modern biological view is that the trypanosomes are members of an intraspecific unit, and that they have originated from *T. brucei*, probably from some antelope strain.

Geographical distribution.—Rhodesian trypanosomiasis occurs in North-Eastern Rhodesia, especially in the Luangwa Valley, about the southernmost limit, 14° S.; throughout Tanganyika Territory; in Portuguese East Africa; in Nyasaland, especially in the region south and west of Lake Nyasa: in fact, its distribution closely corresponds with that of *G. morsitans* in East Africa. (Map I.) A virulent outbreak at Mwanza, Tanganyika, was transmitted by *G. swynnertoni*.

Ætiology.—In human blood (Fig. 20-7, 2), *T. rhodesiense* is morphologically indistinguishable from *T. gambiense* and *T. brucei*: but if it is passed through the rat or guinea-pig, a small but variable proportion of the parasites, especially the stumpy forms, will be seen to have their nuclei located posteriorly to the kinetoplast—that is to say, at the non-flagellar end of the organism (Fig. 20-3, 4, 5, 6). This feature, formerly considered specific, is not now regarded as important, because similar changes are undergone by other trypanosomes.

A good deal of work has been expended in attempting to prove and disprove that *T. rhodesiense* is no other than a strain of *T. brucei* inoculated into man. When injected into rats, *T. brucei* exhibits the same proportion of posterior-nucleated forms as *T. rhodesiense* (Bruce). Taute and his fellow-workers disproved this conclusively by inoculating themselves and 129 native porters with dog's and mule's blood containing *T. brucei*, with a negative result, while rats, dogs and a goat, inoculated with the same blood at the same time succumbed. In 1936 Sicé proved polymorphism and posterior-nucleated forms existed in *T. gambiense*.

In this connection it is necessary to explain what is known as the "Tinde Experiment" as related by Willett and Fairbairn which is a study over 18 years of cyclical transmission. The exact relations between *T. rhodesiense* and *T.*

brucei has been a matter of controversy for 40 years, but now appears to have been settled by the isolation of the former from the bushbuck.

The experiment which was initiated by Corson in 1934, when he began a series of cyclical transmissions through sheep, has been continued uninterruptedly by his successors. The results are described up to the end of 1953 when the strain has been transmitted through 115 sheep as well as through side-lines, such as antelopes and monkeys. During the course of this work yearly tests were made of the infectivity of this strain to man.

The main *sheep* line of *T. rhodesiense* remained infective to man during the whole period when some 138 volunteers were inoculated with positive results in each batch tested.

During the course of this time the incubation period in man has been steadily increasing, which indicates that the virulence of the strain is decreasing. The antelope line, on the other hand, has retained its infectivity to man with frequent fluctuations. The simian line has shown little variation in infectivity, but its virulence for monkeys has increased progressively.

Pathology.—The visceral lesions of *T. rhodesiense* trypanosomiasis are probably more often fatal than lesions of the central nervous system. Hawking and Greenfield (1941) described extensive trypanosomal effusions in pleural, peritoneal and pericardial cavities, associated in the latter

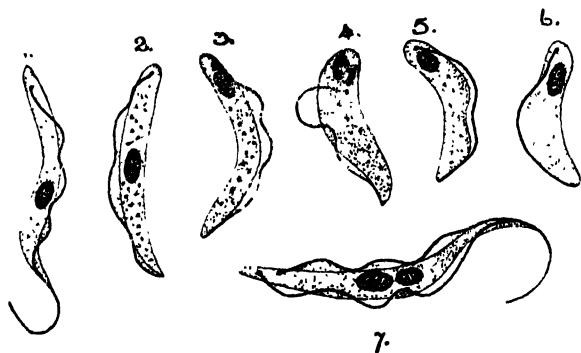


Fig. 20.—Forms of *Trypanosoma rhodesiense*. (After Laveran.)

1, 2, Normal forms in blood of man; 3-6, various stages of posterior displacement of the nucleus; 7, a dividing form.

instance with inflammation of myo-, epi- and endocardium. The cerebro-spinal fluid contained numerous trypanosomes, but the lesions in the nervous tissue were singularly slight, being limited to a histiocytic infiltration of the cerebral membranes. The cell count and protein content were not much raised.

Symptoms are similar to those evoked by *T. gambiense*, though febrile paroxysms are more frequent, and severe glandular enlargement is not often met. The disease generally runs a much more rapid course, and fatal symptoms usually supervene within a year of infection, death taking place from convulsions. Acute mental symptoms, such as mania, are frequent.

Buchanan observed that rapid emaciation, weakness, fever and cedema constitute the most obvious signs of toxic action resulting from this

infection, while careful observation on the heart showed that in nearly every one there is a marked effect on the cardio-vascular system, with irritability and tachycardia. The characteristic erythematous rash is usually marked.

The course of the infection is usually so rapid that patients succumb before the sleeping-sickness stage develops.

Lamborn and Howat (1935) recorded that very mild and almost symptomless infections may occur in natives of Nyasaland. The parasites are quite numerous in the bloodstream, but are not seen in the glands or cerebro-spinal fluid. On inoculation into animals a virulent infection ensues. Similar cases were reported by Woolf in the valley of the Rovuma River in Tanganyika in 1910, and it has been shown that these symptomless carriers may be the starting point of an outbreak.

Diagnosis is the same as for *T. gambiense*. In acute cases trypanosomes are plentiful in the peripheral blood and diagnosis can readily be made by examinations of thick drop specimens. Possibly the parasites are more easily demonstrated by lymphatic-gland puncture. Thus, Kleine found, in a series of 32 cases, 24 had trypanosomes in their glands and blood; 4 in the glands, but not in the blood; and 4 in the blood only.

Corson proved, in a self-inflicted experiment, that a local circular erythema with a darker and slightly tender centre is a useful indication of an infective bite by glossina in light-skinned people.

The treatment with antrypol (*germanin* or *suramin*) is hopeful in the early stages and remarkable successes have so far been recorded; in fact the drug appears to exert a much more immediate action than in *T. gambiense* infections. Dye, in Tanganyika Territory, advised intravenous injections on the first, third and fifth days, and subsequently at intervals of five to seven days till a total of 7 grm. has been administered, and claimed the disappearance of the trypanosomes from the peripheral blood took place within twenty-four hours. In these early cases, with normal C.S.F., too, Gelfand and Alves comment upon the brevity of the period of treatment and the ease of administration of pentamidine. The patient should be kept in bed as far as possible. They administered the drug in doses of 400 mgm. on the first, 300 mgm. on the second and third days; then 250 mgm. daily for 6 days. The response is rapid and the pentamidine is injected intramuscularly. The whole period of treatment lasted eight weeks.

TREATMENT

Tryparsamide and other preparations (*see* p. 113), which are of use in *T. gambiense* infections, appear to be relatively powerless in *T. rhodesiense* cases, but tryparsamide has been used along with antrypol (*suramin*) with success. Unfortunately, some of the apparently cured cases which were recorded have subsequently relapsed. Recent reports indicate that "melarsen B," or arsobal, is the most active drug in this trypanosomiasis.

Apted (1957), after four and a half years' experience in Tanganyika with "Mel B" (abbreviation for arsobal), has reported favourably on this drug in the apparently incurable late stages of rhodesiense infection.

Those with over 40 mgm./100 ml. of protein in the C.S.F. had been classified as incurable, and it was shown that arsobal is a most valuable drug in these

apparently hopeless cases. The death rate over the whole series of 176 cases was 10 per cent. It is notable that patients in poor physical condition are unable to withstand even moderately high dosages between 2.5 ml. and 5 ml. at the commencement of treatment. Many who relapsed respond to second courses and remained well for long periods. The early-stage patient can be cured by a single injection of 3.6 mgm./kgm. body weight (5 ml. for the average adult), though there is some risk, since antrypol continues to give satisfaction in early cases. The best results were obtained by the following schemes:—

- (a) 3 injections of 1.8 mgm./kgm.—Two weeks interval—then 3 injection of 3.6 mgm./kgm.

Average total dosage = 22.5 ml.

- (b) 1 injection of 1.8 mgm./kgm. + 2 injections of 3.6 mgm./kgm.—Two weeks interval—then 3 injections of 3.6 mgm./kgm.

Average total dosage = 27.5 ml.

Melarsen oxide/BAL is presented for use as a 3.6 per cent. solution in propylene glycol. A dose of 5 ml. of this solution is equivalent to 3.6 mgm./kgm. for a patient weighing 50 kgm. Friedheim and Geigy find that *T. rhodesiense* is usually resistant to tryparsamide, but sensitive to “mel B” and in this feature it can be distinguished from *T. gambiense*.

Prophylaxis.—Prompted by his investigations of the hypothesis that big game act as a reservoir for *T. rhodesiense*, Yorke advocated the extermination of this fauna, but recent investigations tend to show that these conclusions were premature and that only certain species such as the bushbuck are dangerous. Jack, in Southern Rhodesia, studying the behaviour of *G. morsitans*, found that the fly was attracted to man by stimuli of movement or scent. Dark colours were most attractive, especially black. White clothing appeared to have some protective value.

Other prophylactic measures are the same as those advocated for *T. gambiense*. (See p. 116.)

Prophylactic injection of antrypol.—Duke (1934) showed by experiments on human volunteers that the prophylactic action of antrypol is more effective against *T. rhodesiense* than *T. gambiense*. (See p. 116.)

Pentamidine prophylaxis as for *T. gambiense*, together with bush clearance, is being employed on the shores of Lake Victoria and on the Ruanda-Urundi borders of Tanganyika.

For further details of African trypanosomes, see Appendix, pp. 905-914

II. SOUTH AMERICAN HUMAN TRYPANOSOMIASIS

Synonym. Chagas' Disease.

Definition.—Usually an acute, more rarely a chronic disease, caused by *Trypanosoma (Schizotrypanum) cruzi*, and disseminated by certain reduviid bugs. The acute stage of the disease is characterized by diarrhoea and enlargement of lymphatic glands and spleen, accompanied by cerebral symptoms. The chronic form may manifest special symptoms, according as the heart or other important organs are most invaded by the parasite.

Geographical distribution.—In the provinces of Minas Geraes, São Paulo, Rio Grande do Sul, and Goyaz in Brazil; in the states of Trujillo and Miranda in Venezuela; and in the Western Argentine in



MAP II
South America, showing distribution of S. American
trypanosomiasis (Chagas' Disease)

Tucuman and Jujuy; in children in Cordoba, Argentina, and in the Catamarca province. (Map III.) The disease has also been found in Panama and in Guatemala, in Bolivia, Peru, Ecuador, Chile (provinces of Tarapacti and Jurico), in Venezuela, San Salvador, in Uruguay, Colombia, and in Mexico, New Mexico and S. Texas in U.S.A. In fact almost the whole S. American continent, with the exception of Honduras and the Guianas.

Trypanosoma cruzi, or trypanosomes resembling it, have been found in bugs (*Panstrongylus*, *Triatoma* and *Rhodnius*) in California and in Texas,

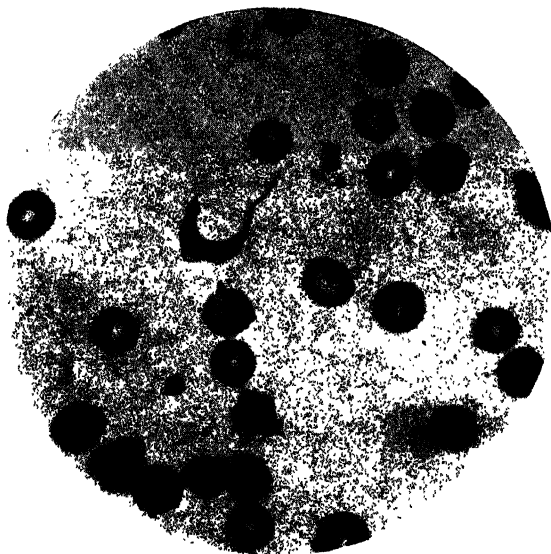


Fig. 21.—*Trypanosoma cruzi* of Chagas' Disease.
Note circular shape and spherical karyosome.



Fig. 22.—*Trypanosoma cruzi*: schizogony in heart-muscle.
(From a preparation by J. Gordon Thomas.)

but they apparently do not transmit the disease to man in these regions. *T. cruzi* has been found by Malamos and others in Macaque monkeys imported from India.

Ætiology.—During the febrile attacks the parasite, *T. cruzi*, can be found only sparingly in the blood, though in the acute disease, as seen in children, it is more abundant. In chronic cases, in which the clinical symptoms may be puzzling, parasites are apparently absent. Apparently in human beings this is a disease of childhood, but in Panama a case has been found by Ludeberg in a man of seventy-seven.

This trypanosome was at first referred to a separate genus, *Schizotrypanum*, on account of its distinctive method of multiplication in the human body. Instead of the longitudinal division which occurs in other species of trypanosomes, this parasite proliferates in the cells of the internal organs, especially in the interior of striated muscles, such as the heart. Two forms, one slender, the other broad, are found in the peripheral blood. In the internal organs multiplication takes place by schizogony (Figs. 21, 22) at a very rapid rate, the resulting forms resembling leishmania bodies which, four days later, become transformed once more into trypanosomes that invade the blood-stream. (For a complete account of the parasite, see Appendix, p. 910.) This trypanosome, as it occurs in the blood, can be distinguished from other human trypanosomes by its peculiar "C"-shape, and by the oval appearance of the kineto-nucleus. Dividing forms are never seen in the blood. It is by no means certain whether it is related to, or identical with, *Trypanosoma vespertilionis* in bats.

T. cruzi is easily cultured on N.N.N. medium, in which it assumes the stunted forms usually seen when it is found in its definitive hosts. Tang (1953) has been able to grow *T. cruzi* in tissue culture in which it follows the pattern of cycle as in the mammalian host.

The reservoir-hosts of *T. cruzi* are animals peculiar to the country in which the disease occurs; there are various species of armadillo, opossum rodents and others (see Appendix, p. 912).

It is possible that closely related trypanosomes—*T. rangeli* and *T. ariarii*—may also be responsible for a certain number of cases (Fig. 271) (see p. 913).

It is now known that infection with *T. rangeli* is widespread in Venezuela where Pifano has found it in dogs, opossums and in a large number of humans, often in association with *T. cruzi*.

Transmission.—The adult trypanosomes are ingested by the intermediary invertebrate host, the bug, *Panstrongylus megistus*, either in its larval, nymphal, or adult stage (Fig. 444, p. 1088). After they have passed through many stages in the intestinal canal, in a period of 8–10 days, fully formed trypanosomes, known as "metacyclic" forms, re-appear in the hindgut and are passed out through the faeces of the insect. Infection of man, therefore, probably takes place when the insect defæcates into the wound caused by its bite. Mayer stated that infection may be conveyed through the bug in a hereditary manner. In the Northern Argentine the common host appears to be the "Unchuca" (*Triatoma infestans*); in Uruguay *T. rubrivaria*, but many other species of the genera *Panstrongylus*, *Rhodnius*, *Eratyrus* and *Triatoma* can transmit the infection (see Appendix, pp. 1083–1084).

Congenital transmission of *T. cruzi* is probably quite common. Romaña, Vasvari and Rothe (1953) found parasites in the blood of a fifteen day infant in the city of Salta, Tucuman, Argentine. A number of observers in Brazil have reported on the transmission of Chagas' disease in the course of *blood transfusion*. With a view to preventing such accidents experiments have been conducted on the sterilization of blood infected with *T. cruzi*. The best results have been obtained with gentian violet in a concentration of 1 : 4000 which kills the trypanosomes in the blood after an exposure of 24 hours. It is recommended that the blood of donors suspected of harbouring *T. cruzi* should be treated prophylactically with this amount of dye 24 hours before transfusion.

Pathology.—The post-mortem appearances have been described in children. The heart is usually enlarged and there is an excess of yellow or greenish pericardial fluid, sometimes containing a few fibrinous flakes. In microscopic sections there is evidence of diffuse myocarditis and between the muscle fibres there is extensive infiltration of lymphocytes, plasmacyt macrophages and round cells. There is enlargement of the spleen, parenchymatous degeneration of the liver, and general enlargement of the mesenteric glands. The thyroid gland, as a general rule, is congested and hypertrophied. There is general infiltration of the subcutaneous tissues and thickening of the serous membranes. Subserous ecchymoses are common, and small hæmorrhages in the brain and spinal cord have been described. The skeletal muscles appear to be the seat of election for multiplication of the parasite, and the changes are essentially similar to those in the heart. The gross lesions in the various organs are due to the presence of the parasite. Under the microscope, cyst-like cells, containing leishmania forms, can be found, particularly in the striated muscular fibres, and in those of the heart. When the suprarenal glands are affected, pigmentation of the skin and other evidence of Addison's disease have been observed. The blood does not show great changes, as a rule, but in the acute stages considerable leucocytosis with mononuclear increase has been recorded.

Symptoms.—Attention has been drawn to a primary lesion—termed by South American observers a *chagoma*—which results from invasion of the skin and surrounding tissues by proliferating trypanosomes. This takes the form of a local inflammatory swelling, in which leishmanial forms of the parasite multiply within the fat cells. This is followed by a centripetal lymphangitis with formation of nodules along the path of the vessels.

Mazza and Freire described similar lesions which they considered hæmatogenous as well as cutaneous swellings, the size of olives, adherent to the skin, in the suprahyoid, pectoral, and other regions. On the chest they may be as long as 8 cm., raised above the level of the skin, of cartilaginous consistency and violet-red. Some fourteen days after the infecting bite a rash may be seen (Mazza and Mizara) on chest and abdomen, consisting of sharply defined red spots, the size of a pin's head. There is no pain or itching, and the exanthem fades entirely within seven to ten days. Some three weeks from the time of infection cedema of the eyelids, sometimes also of the malar and temporal regions, together with unilateral conjunctivitis (Romaña's sign) is noted (Fig. 28). There are some reasons

for believing that occasionally the conjunctiva may be the port of entry for *T. cruzi*, as E. Chagas has shown experimentally (by placing the excreta of bugs on the rabbit conjunctiva). Furthermore, in an accidental laboratory infection recorded by Herr and Brumpt, the site of entry was undoubtedly the conjunctiva, and infection was followed by dacrocystitis, swelling of the face, pyrexia and adenitis. According to Talice and Rial dacrocystitis may be uni- or bilateral and is invariably accompanied by facial cedema. The reaction is therefore allergic in the region where reduviid bugs deposit infected faeces during sleep.

Enlarged lymphatic glands containing leishmania forms of *T. cruzi* are described by Mazza, in association with the inoculation chagoma, in satellite lymphatic dissemination, as well as generalized lymphadenitis.

The further course of the disease is at present rather obscure. Chagas (1934), in an experimental inoculation of a patient suffering from incurable malignant disease, observed no outstanding manifestations beyond intermittent pyrexia. Trypanosomes appeared in the blood on the thirty-eighth day.

Chagas and his colleagues described an *acute form* with pyrexia, especially in infants, with general anasarca and thyroid enlargement, and sometimes also with general lymphadenitis. The liver and spleen may both be enlarged. In the terminal stages the child develops symptoms of meningo-encephalitis. Mazza and his colleagues describe an intermittent quotidian type of fever with a double peak as strong presumptive evidence of Chagas's disease. Intermittent fever persists as long as the trypanosome is present in the blood. The *chronic form*, according to Brumpt, may assume a myxoedematous, cardiac or nervous complexion. The former is frequent in children up to fifteen years of age and is characterized by thyroid insufficiency, scanty urine and dry skin. The cardiac type is characterized by cardiac arrhythmia and extrasystoles with brachycardia; the nervous type by intention tremor and various paralyses.

The frequency of sudden death from heart failure in men over 40 is giving rise to great concern in Brazil and is due to destruction of the conducting fibres in the heart and to nests of schizogonic parasites in the heart muscle. Céspedes and Aguilar (1955) have had 20 cases of Chagas' disease in Costa Rica, three of which were fatal due to myocarditis. In an acute fatal case of a 17 year old male the outstanding feature was cardiomegaly with gallop rhythm without signs of valvular disease. Acute myocarditis was present with parietal thrombosis in the left ventricle with dilatation in all cavities. Dias and Laranja (1954) find that electrocardiographic abnormalities are three times more frequent in the endemic areas than elsewhere. In 410 electrocardiograms 15.8 per cent. were abnormal. (R,B,B,B, A.-V, block, ventricular premature contractions.)

Kraus has pointed out that it is difficult to distinguish endemic goitre and

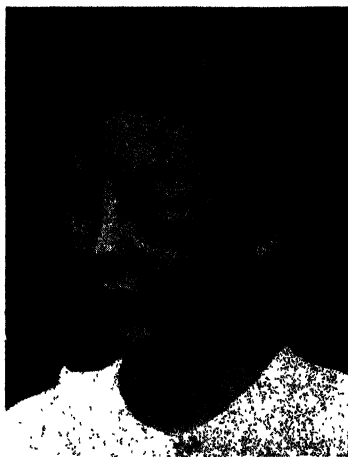


Fig. 23.—Unilateral palpebral cedema (Romana's sign) in Chagas' Disease. (Dr. S. B. Pessoa, São Paulo.)

cretinism, which are frequent in the geographical range of this disease, from acute and chronic trypanosomiasis as depicted by Chagas. Munk has found that in Brazil, where Chagas made his observations, 75 per cent. of the population normally have goitre and there is a cretin in almost every family.

In a recent review of the cardiological aspects by Laranga, Dias, Nobrega and Miranda (1956) it is stated that acute cases show enlargement of the cardiac shadows, particularly on the left, during the sixth week of infection. In the chronic stage it is the most common cause of advanced A-V block in a patient under 50. The clinical history is most important. Complement-fixation tests are more trustworthy than xenodiagnosis. At autopsy there is enlargement of all the cardiac cavities, hypertrophy of the myocardium with diffuse inflammatory changes, rarely extending to the endocardium. In patients over 40 there is usually coronary atherosclerosis, with atheromatous obliterative changes in the small and medium-sized branches of the coronary arteries. Myocardial ischaemia is probably an important mechanism in the development of chronic Chagas' disease. Acute Chagas' heart disease is a reversible type of parasitic heart disease. In its early stages chronic Chagas' heart disease, in patients under 20, may be difficult to differentiate from rheumatic carditis.

Mal de Engasco (or suffocation disease) is a term applied to a novel syndrome which may be described briefly as *Megaoesophagus* and *Megacolon* (Köberle and Nador, 1955). The essential lesion is destruction of the *plexus myentericus* of Auerbach in the muscular coats. Later reports, based upon a study of serial sections from 20 cases, suggest that there is a pathologic widening of other muscular tubes, such as the stomach, duodenum and ureter. Therefore dilatation of tubular organs with muscular hypertrophy definitely represents one of the main manifestations of Chagas' disease. Metastases of parasites into these organs leads to rupture of the pseudocysts and to granulomatous inflammation in the interior of the muscular layer and by lymphatic spread leads to destruction of the nerve plexuses resulting in dyscoordination of the peristaltic movements and achalasia of the cardiac sphincter. It may also account for the myocarditis described above.

Diagnosis.—The trypanosome is usually present in very small numbers in the bloodstream, and prolonged search may be required. It may be necessary to collect the blood in citrated saline and subject it to lengthy centrifuging. The parasites may sometimes be found in the cerebrospinal fluid by lumbar puncture, but puncture of the lymphatic glands or of spleen, bone marrow occasionally reveals them. A readier method of diagnosis is to inoculate a guinea-pig with the patient's blood; the developmental stages of the parasite may be found subsequently in the organs. In the acute form positive results are said to be obtained in 26 per cent. of cases, but in chronic cases animal inoculation is negative.

These difficulties in diagnosis have led to the elaboration of a complement-fixation test (Machado, Villela and Bicalho). The antigen is prepared from a glycerin extract of heart and spleen of infected animals. Lacoste, using a glycerin spleen extract of infected puppy, recorded positive reactions in 68.5 per cent. (Machado). Artificial cultures of *T. cruzi* have provided a more reliable antigen. The latest method is with Davis's modification of suspensions of the

cultures with merthiolate and later with benzene and with chloroform. Unti and da Silva regard this test, (or the Machado-Guerreiro reaction) as the test; positive results being registered in more than 97 per cent. The specificity of the test against other forms of human trypanosomiasis must be accepted with reserve, but it seems evident that there is no parallelism between the Machado and the Wassermann reactions. An intradermal test was introduced by Mayer and Pifano, using an extract, "Cruzin," prepared from cultures of *T. cruzi*.

Brumpt suggested a method of xeno-diagnosis which consists in feeding laboratory-bred *Panstrongylus* with the blood of the suspected person, and demonstrating the cyclical development of the trypanosome in the intestinal tract. Borzone's modification of Brumpt's method consists of collecting 10 ml. of blood in a dry syringe. It is then placed in a watch glass and 4-6 larvae of *Triatoma infestans* are fed on it under cover in a bell-jar which is kept in darkness. When engorged they are set apart at 37° C. and their faeces are examined from time to time during two months.

Nussenzeig and Sonntag (1952) employ a new method of artificial xeno-diagnosis. They use an open cardboard box containing *Triatoma vitticeps* covered with gauze and placed in a jar. About 10 ml. of blood to be tested are collected in a Borrel's cylinder (or jar) the mouth of which is closed by a piece of moistened cowgut. After heating in a water bath at 37° C for 10 minutes the flask is inverted, and placed in the jar, so that the membrane is in contact with the gauze of the box, thus enabling the bugs to feed on the blood.

Differential diagnosis.—On clinical grounds, Chagas' disease is to be distinguished from endemic goitre, ancylostomiasis, Graves's disease, cretinism, myxoedema, Addison's disease, and other disturbances of the endocrine glands.

Treatment.—The treatment of Chagas' disease is still in a very unsettled and unsatisfactory state. All the drugs which have so far been employed for the cure of African trypanosomiasis have been tried and failed. The hopes pinned upon the two Bayer compounds—7602 (ac), a quinoline, and 9786 (as), an arsenical, have failed. Now we have turned to the antibiotics. Pizzi, Prager and Knierim (1953) have shown that achromycin (then called *puromycin*) had some effect on the *T. cruzi* in mice and so also had primaquine. Sonntag and Kloetzel have more or less confirmed these conclusions, working also with mice and suggest that the time has arrived for trials in human cases. Seneca, Kane and Rockenbach (1952) have found that a new antibiotic—*Rimocidin*—produced by *Streptomyces rimosus*, which is also the parent of terramycin, exerts a lethal action upon *T. cruzi* in culture within 24 hours.

Prophylaxis.—This should be directed principally to the suppression of the insect concerned—*Panstrongylus* (*Triatoma*) *megistus* (Fig. 444, p. 1083.) This is a large black insect belonging to the family Reduviidae, well known to the natives, who call it "barbeiro," because, presumably, of its fondness for the face.¹ The nymphs bite and can convey the infection, but the adults, having wings, are more dangerous. In the daytime they live in the grass walls and roofs of the dirty native houses, or of pigsties, coming out after dark in search of their food—blood. Their habits indicate better and cleaner housing, sleeping off the ground, and protection by mosquito-netting. DDT and BHC have been used for destroying reduviids

¹ To Americans these insects are known as "kissing-bugs" because of the lesions they produce on the eyes and lips.

(Chapter LII). Pelloux speaks highly of SNP (Thiophosphate-o-diethyl-o'-paranitro phenyl) either in emulsion or dust. The former in 1 per cent. solution at the rate of 200 ml. per sq. m. kills triatomata.

Pinotti and his staff (1954) have done an immense amount of work in Brazil in the control of Chagas's disease. The programme has been carried out by the National Malaria Service. Up to the end of 1952 181,498 houses in 24,718 areas in 548 counties were inspected and of 145,180 triatomid bugs, 56,780 were examined for *T. cruzi*. Complement fixation tests were found positive principally in the centre and south, especially in Minas Geraes and São Paulo. There the disease is a serious problem. Up to the end of 1952, 241,095 houses and their outbuildings were sprayed with BHC at a minimum dose of 500 mgm. Gamma isomer per sq. m. One application yearly maintains the triatomids at a low level, but ideally two such applications prove necessary for eradication.

The fact that the armadillo is the reservoir-host suggests that human habitations should be placed as far away from the burrows of these animals as possible, and that the floors of the houses should be constructed so that the armadillo cannot burrow underneath them. Brumpt has called attention to the fact that one form of reduviid, *Panstrongylus geniculatus*, which normally feeds on the armadillo, is commonly met with in the burrows of a Rock, or Moco, cavy, *Kerodon rupestris*, and that the trypanosome can be found in these bugs at great distances from any human habitation. Spontaneous infection of local armadilloes has been reported. It is, therefore, possible that the disease exists independently of man. Robertson also found large numbers of this trypanosome in the blood of an opossum (*Didelphis*) in Honduras. (See also p. 912.)

CHAPTER VI

LEISHMANIASIS

UNDER the title "Leishmaniasis" at least three diseases are included—Kala-azar, Oriental Sore, and Espundia. (Map III.) These, though clinically quite distinct and having each a definite topical and geographical distribution, are all associated with what, optically, at any rate, appears to be the same organism, *Leishmania*.

I. KALA-AZAR (VISCERAL LEISHMANIASIS)

Synonyms. Tropical Splenomegaly; Black Sickness; Sirkari Disease; Sahib's Disease; Burdwan Fever; Dum-dum Fever; Ponos (Greece); Mard el Bicha (Malta).

Definition.—An infective disease characterized by chronicity, irregular fever, enlargement of the spleen and often of the liver, and the presence in these and other organs of *Leishmania donovani*.

Geographical distribution.—India—Assam, Madras—along Ganges and Brahmaputra. China—N. of Yangtse R. between coast and line joining Peking-Hankow; Provinces of Kiangsu, Shantung, Chih-li, north to Jehol, Fengtien, S. Manchuria and Mongolia. S. Canton. Sudan—Kassala and Blue Nile districts. Abyssinia—S.W. Omo river and N. of L. Rudolf. N. Kenya—Uaso Nyiro river and Nairobi-Addis Ababa road, Kitui reserve, Tseikuru, Buringo District, Kerio River, Lake Hannington. Italian Somaliland near Cape Gardafui; Senegal, Dakar, Chad and French Niger Territory, Gambia (Gunjur), N. Nigeria, French Guinea, Cameroons, Congo, Tunis, Tripoli, Morocco, Algeria, Egypt (rare), Sicily (Catania), Italy (Gargano Promontory, Adriatic Coast), Corsica, Crete (Canea), Spain (Madrid E. and S. Coasts), Portugal, Turkey, Hungary, Roumania, Bulgaria, Yugoslavia, Cherbourg, S. France (Marseilles), Greece (Messinia and Peloponnese), Athens, Salamis, Macedonia—Salonica, Drama, Serres, Kavalla, Grecian Archipelago, Malta, Iraq, Transjordan, Saudi Arabia (Tarizzo), S. Arabia (Yemen), Russia W. and E. of Caspian, Transcaucasia and Turkestan, Persia (Reid), Shiraz, Abadan, Persian Gulf littoral. In the East of U.S.S.R. it is found in Ili and Alma-Ata in Kazakitan, Fiume and Osh in Kirgizia and Kulyab and Tadzhikistan. It is the most northerly point yet recorded.

S. America—N.E. Brazil, Sergipe—Araca-ju, N. Bolivia, N. Argentine, Chaco, Oran, Tabacal, Paraguay, Colombia, Venezuela—States of Guárico and Bolívar, Guatemala (Cabrera), Surinam (Winckel). A few cases have been found in Mexico (Baéz), and in El Salvador by Álvarez in 1955.

Epidemiology.—The main information on epidemiology has been gained from the Assam epidemics which, beginning about 1870, have recurred at irregular intervals since. The epidemic advanced slowly along the Brahmaputra

Valley at the rate of some hundred miles in seven years. Its introduction into a village has usually been traced to some individual from an infected locality. Generally it clung to a place for six years and then disappeared without any apparent change in local conditions. A house seemed to retain the infection for many months, and natives considered it dangerous to re-occupy under a year. In 1922-3 it extended up to the headwaters of the river at Dibrugarh where it had never been known before.

At the present time kala-azar is very rare and confined to Assam, Bengal, Bihar and Orissa and the United Provinces as far as Lucknow. It stretched patchily down the East Coast of India as far as Tuticorin.

On account of its deadliness in Assam, kala-azar, as it swept onwards, became a terror to the natives. Those suffering from the disease were turned out of the villages; sometimes they were made unconscious with drink, taken into the jungle and burnt to death. Some villages cut off all communication with neighbouring ones for fear of infection; other villagers deserted their homes and even migrated to a different district.

The neotropical form occurs in various types of country—in miserable hovels, in dense forests, in desert country and on river banks.

Kirk has found that the patchy distribution in the Sudan resembles the epidemiological features of the S. American disease.

The outstanding epidemiological features of the disease in India and China are that it is confined to rural districts, especially alluvial plains, and does not usually occur above 2,000 feet. The temperature conditions are a monthly mean maximum below 100° F. and a monthly mean minimum above 45° F. In India a high degree of humidity is a common factor: not so in China. In the Mediterranean the greatest number of cases occur from March to May; in Assam, in the cooler months, from November to February; in the Sudan, after the rains between August and December; in China no seasonal incidence has been observed.

Napier stated that an outbreak is usually determined by a concatenation of climatic and other factors such as widespread distress after an earthquake or an influenza epidemic which determine a general increase of cases. When all susceptibles, especially the children, have been attacked, all those in fact who were spared from the last epidemic, then and then only the disease dies down. For further information the reader is referred to p. 135 where the animal associations of kala-azar are discussed.

An outbreak of infantile leishmaniasis has been discovered in the Craiova district of Roumania as well as in the Vidin and Lom districts of Bulgaria (Minulescu, 1956).

Varieties of Leishmania.—In 1904, leishmaniasis was discovered in Tunis by Cathoire, and important studies by the Sergeants, Nicolle, and many others showed that the parasite occurs in many of the islands and countries in the Mediterranean basin, especially Sicily, Greece and Crete; that there it is usually confined to young children is known as *ponos* or infantile kala-azar, the parasite of which has been considered a distinct species; and, further, that, whilst in India dogs are seldom affected, in the Mediterranean basin and in Spain very many of these animals are naturally the subjects of leishmaniasis (*L. caninum*), and in most cases are closely associated with the infantile human disease.

Adler and Theodor have stressed differences between Mediterranean and Indian kala-azar; in the Mediterranean, children under one year are attacked, while in India kala-azar in infants is uncommon. (It must not, however, be thought that Mediterranean adults are always immune.)

In the Mediterranean area it is a seasonal disease both in infants and in dogs. On the outskirts of towns and villages it usually appears in April but is very rare after November. In China, too, it has been observed that children are infected solely in the sandfly season. Thus, if a child be born in October, the first signs may be observed in the following August.

Nicolle differentiated the parasite, which is morphologically indistinguishable from *L. donovani*, as *Leishmania infantum*, but Brumpt considered that this type is normally a parasite of the dog (*L. caninum*). The resistance of *L. infantum* to antimony therapy was remarked upon by Adler.

This close association between the canine and human disease is not invariable; dogs are commonly found infected in Morocco and Algiers where human kala-azar is very rare; in Teheran (Persia) the canine disease is very common: the human disease unknown. In Iraq where human kala-azar is very rare, and where canine leishmaniasis was thought not to exist, it has recently been found in a pack of foxhounds (1957). No canine infection has been found in India (after an examination of over 2,000 in Madras).

The canine form is more widespread than formerly supposed; in China, for instance, it has been found in Peking as well as in Manchuria (*see also* Appendix, p. 918).

Infected dogs can be recognized by their extreme emaciation, and thickened and ulcerated skin.

In India kala-azar also occurs amongst infants and Napier has reported it in a child less than eight months old. In Bengal the peak of age-incidence is eighth to tenth year in girls and from tenth to twelfth year in boys.

Kala-azar may suddenly break out where previously unsuspected. Thus, Schretzenmayr described a sudden outbreak at the beginning of 1938 amongst Chinese troops in Canton, where the disease had not been previously noted. The first case was diagnosed through the discovery of leishmania in a malaria patient, and during the next five months a further 83 cases were identified. The disease appeared to follow the usual course, but in a number of cases jaundice was a feature. Sudden outbreaks have also been recorded in Nigerian troops in Northern Kenya and Southern Abyssinia during the second world war. One half of patients admitted to hospital died.

The parasite of kala-azar in S. America was first demonstrated by Migone in Paraguay in 1913 and subsequently the routine use of the *viscerotome* by da Cunha and Chagas in 1936 in the search for yellow fever, brought many others to light. At first Brazilian workers separated the parasite as *L. chagasi*. In its main features it resembles the Mediterranean form.

The first case of what is known as kala-azar occurred in a German soldier who contracted the disease in Peking in 1900 and died later in Germany. Peculiar intracellular bodies were found in preparations of spleen, liver and bone marrow and were demonstrated at the Leipzig Medical Society in February, 1903, but nobody could give a satisfactory explanation of them. It was not till Leishman's announcement later in that year that these bodies were actually parasites that Marchand and Ledingham in 1904 realized the nature of the bodies they had seen in Germany.

Ætiology.—The kala-azar parasite (Plate VI) is included by most

authorities in the genus *Leishmania* (though it is morphologically indistinguishable from the genus *Leptomonas*). Two stages are recognized, intracorporeal and extracorporeal. The parasites grow and multiply within the host cells in the spleen, bone marrow and lymph glands. They are transported along protoplasmic processes which pass from cell to cell. They may also be liberated from disrupted cells and taken up by others. Parasites are also taken up by leucocytes and enter the bloodstream, where most of them are destroyed, although they may survive in numbers sufficient to be detected by blood culture.

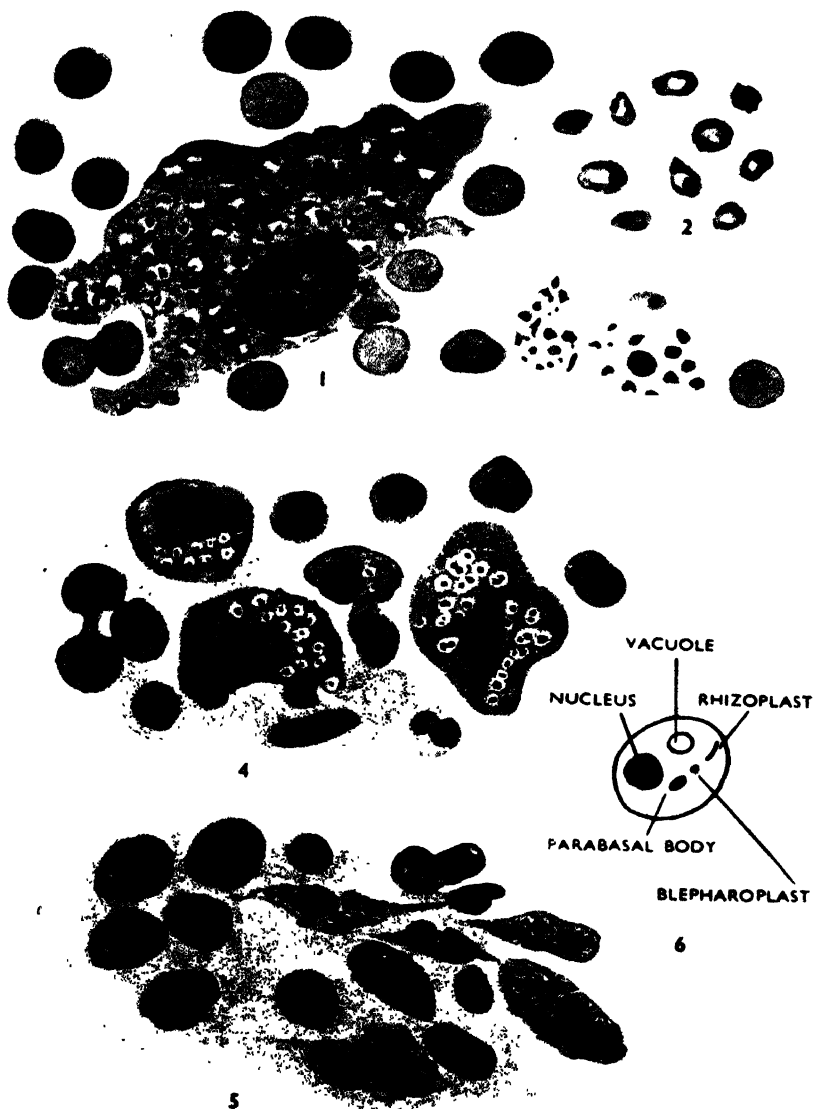
Leishman-Donovan bodies are typically parasites of the reticulo-endothelial cells. The parasite is a small ovoid or roundish organism measuring 2-4 μ in diameter. When stained according to Leishman's method it shows two lilac-coloured chromatin masses, one larger than the other, enclosed in a cytoplasm having a faint bluish tint about the periphery. The larger is the trophonucleus; the small rod-like body is the rhizoplast. It divides by longitudinal fission.

In smear preparations the parasites are often free or in clusters of various numbers, sometimes arranged with great regularity like the merozoites in the segmenting quartan or tertian malaria parasites. Sometimes as many as 50 to 200, or even more, are found together embedded in a structureless matrix or stroma, the remains of the original host-cell.

The parasite can be cultivated outside the body. The medium used by Rogers was citrated blood. When kept at blood-heat the parasites degenerate and disappear, but at a temperature of 20-22° C. they multiply rapidly and assume an elongated motile flagellated form. The flagellum arises from the rhizoplast and projects at the anterior end of the body as in *Leptomonas*, but there is no undulating membrane as in trypanosomes. These flagellated forms measure 12-20 μ in length, and multiply by longitudinal fission. They move actively, flagellum foremost, and tend to agglomerate into rosette groups with their flagella directed centrally. The N.N.N. medium is now considered the best for culture, but technique must be particular, as bacteriological contamination rapidly kills the parasites. Reichenow's medium of citrated blood and Ringer's solution is also very suitable. A special medium consists of embryonic hamster tissue, heparinized blood, embryonic fluid and spleen extract. Wenyon succeeded in keeping the parasite alive in successive cultures for fifteen years. The flagellated forms have not been found in the human body, but Wenyon has noted that they may be associated with typical leishman bodies in canine leishmaniasis. The parasite can be communicated to dogs, cats, jackals, monkeys, rats, voles, hamsters and mice, provided that large doses are injected into the peritoneal cavity or into the liver. To infect a dog, it is necessary to inject 2-4 ml. of a thick emulsion of infected spleen, liver, or bone-marrow. Intravenous injection is by no means so successful, while injections of cultures rarely succeed.

It has now been shown that for growth *Leishmania donovani* and *L. tropica* require ascorbic acid, hæmatin and also an unknown substance in the serum.

Transmission of the parasite.—Adler (1940) has made some interesting and suggestive observations during attempts to reproduce the disease in five patients with advanced malignant disease by injecting flagellates from cultures and from the organs of infected hamsters. The incubation period was five months, before it was possible to demonstrate



1, Parasites enclosed in endothelial cells in film from spleen puncture, stained with Leishman. 2, Free forms from spleen. 3, Blood-platelets in same film for comparison. 4, Parasites enclosed within splenic pulp cells, as seen in section, stained with hæmatoxylin. 5, Parasites in histiocytes and endothelial cells in intestinal mucosa. 6, Diagram of Leishman-Donovan body, highly magnified.

LEISHMAN-DONOVAN BODIES IN KALA-AZAR

the parasites in blood or glands. None of the patients developed marked splenomegaly, fever, or other signs of the disease during nine months. The explanation of this anomaly is not at present forthcoming. That kala-azar is primarily a zoonosis has been shown by the discovery of *L. donovani* in jackals in E. Russia and Turkmenistan. It has also been conclusively proved by Heisch and Clinton Manson-Bahr in Kenya that gerbilles and ground-squirrels are reservoir hosts in that country and that the disease can be conveyed from them to man by passage through hamsters (see p. 154).

In many places the dog is considered the chief reservoir of infection, but in China, a small rodent, the striped hamster (*Cricetulus griseus*), has proved in the laboratory to be extraordinarily susceptible, and this animal has once been found naturally infected in the wild state. In Morocco a small squirrel (*Xerus xetulus*) has also once been found similarly infected.

On account of the peculiar topographical distribution of kala-azar in India Sinton first suggested in 1922¹ that a sandfly (*Phlebotomus*) was the insect vector and in the same year Napier found a close correspondence between the distribution of *P. argentipes* and the number of kala-azar cases, and noted that this species of sandfly feeds solely on man. A similar suggestion about the leishmania of oriental sore had already been put forward by Wenyon in 1911 and subsequently proved correct by the Sergeants in Algiers. Since then a large amount of work on the subject has been performed by Christophers, Shortt, Knowles, Napier, Barraud, Lloyd, and Smith, with the result that a very rapid, intensive development of herpetomonas forms was found to occur in one species of sandfly—*Phlebotomus argentipes*—when fed on the blood of patients suffering from kala-azar. The whole midgut becomes infected and in some individual insects the infection spreads to the pharynx, and even to the buccal cavity (Fig. 24). Subsequently it was found possible to transmit the infection to hamsters by artificially infected sandflies in the laboratory and later (1942) Swaminath, Shortt, Smith and Anderson announced the successful transmission of kala-azar by the bites of sandflies to seven human volunteers. This success, after years of fruitless effort, was obtained by sustaining the sandflies during the two weeks of development of the parasite on fruit-juices.

In other endemic centres different species of sandfly are involved: *Phlebotomus major* in Eastern Mediterranean; *P. orientalis* and *P. clydei* in the Sudan; *P. perniciosus* in Western Mediterranean and North Africa; *P. arpaklensis* in Tadzhikistan and Transcaucasia; *P. chinensis* and *P. sergenti*, var. *mongolicus* in China; *P. langeroni* in Sudan; *P. garnhami* in Eastern Africa; *P. longipalpis* and *P. intermedius* in South America.

An account of the bionomics of the sandfly will be found on p. 1035.

Hu and Cash made the most interesting observation that the leishman bodies are taken up by the cells of the reticulo-endothelial system, or clasmotocytes, and these, in experimentally-infected hamsters, become massed as a thick layer of heavily infected tissue lying immediately underneath the skin, though externally no change can be seen. This observation has been confirmed by Hindle and in skin sections from fatal cases of kala-azar a similar condition has been found. All levels of the skin below the epidermis contain leishmania-filled cells collected in large masses about the sweat-glands and arterioles and scattered diffusely

¹ Private communication to Knowles.



Fig. 24.—Section of *Phlebotomus argentipes*, showing pharyngeal infection with *Leishmania donovani*. (From Indian Jl. Med. Res.)

P, lumen of pharynx; P2, posterior termination of pharynx; T, ridges of crinkly portion of pharynx; M, muscles of pharynx; F, flagellate near anterior extremity of pharynx; F2, flagellates anterior to crinkly portion; F3, flagellates breaking free from main mass of growth; F4, massive growth of flagellates at posterior end of pharynx.

throughout the corium. The relationship between this condition and the curious skin eruptions (p. 145) described in India is of interest, and suggests how the parasites may be abstracted by sandflies.

It had been suggested that the transmission may be direct from man to man through the fæces. The evidence for this is based upon the fact that leishmania parasites occur in polypoid masses in some intestinal cases of kala-azar within the intestinal mucosa. Shortt and his colleagues demonstrated Leishman-Donovan bodies in numbers in blood-and-mucous stools in a boy suffering from kala-azar with dysenteric symptoms.

Forkner and Zia in China, on the other hand, discovered leishmania in material obtained by passing a swab over the nasal mucosa of nine kala-azar patients, and parasites were also seen in the material blown from the nose (droplet infection). The tonsils were heavily infected. Material from these situations produced kala-azar in hamsters by intraperitoneal inoculation.

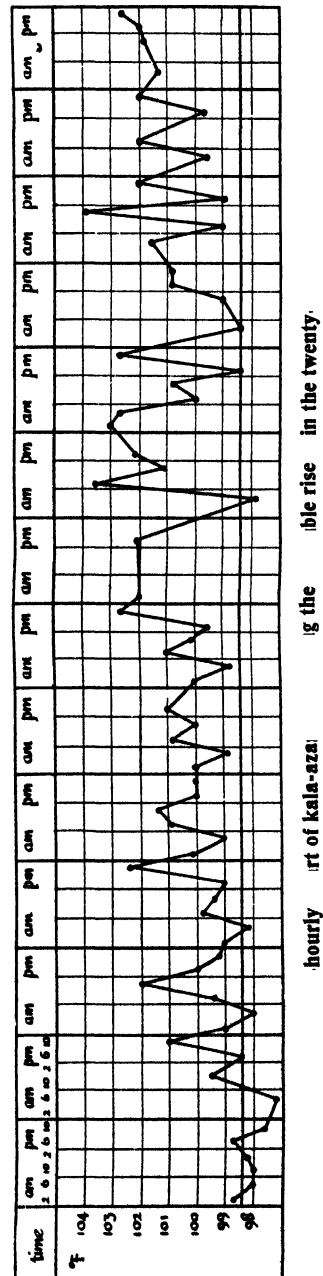
Shortt and Swaminath also reported *Leishmania donovani* in the nasal mucus from cases of Indian kala-azar. In a certain proportion of advanced cases viable parasites are also excreted in the urine.

In adults infected in the Mediterranean basin, the parasite may remain localized in the regional glands, especially those of the neck which show a sustained painless enlargement.

That kala-azar may occasionally be a congenital infection has been proved by Carmichael Low and Cooke (1926), who diagnosed this disease in a child seven months old, born in England of a mother who suffered severely from kala-azar during pregnancy. The fact that leishmania is a tissue parasite makes it easier to understand the mechanism of congenital kala-azar than that of congenital malaria. Others have been reported by Hindle (1928) and Banerji (1955). Two cases transmitted by blood transfusion have been reported by Chung. A case of accidental infection with *L. donovani* in a laboratory worker, whose finger had been bitten on several occasions by experimentally infected animals, has been recorded by Terry and colleagues (1950).

Predisposing causes.—Kala-azar attacks both sexes and all ages but shows a predilection for recently arrived immigrants. In the Mediterranean basin it occurs almost, though not quite, exclusively in children (five months and upwards): in India it occurs at any age.

Pathology.—The spleen is grossly enlarged. In the acute stage the capsule is smooth, thickened and nodular, becoming in the chronic form almost cartilaginous. The splenic pulp is increased in amount and very friable.



There are usually numerous infarctions. The hypertrophy is due to congestion and reticulo-endothelial proliferation; it is estimated that a considerable part of the spleen substance is composed of parasites. There is little fibrosis. The leishmania are numerically more abundant in the spleen than in any other organ.

The liver is also enlarged, brown or mottled, almost nutmeg in appearance. The Kupffer cells are packed with parasites. There is some pressure atrophy of the parenchyma cells and, finally, in the chronic stage, a fine intralobular cirrhosis.

The bone-marrow is reddish, containing abundant parasites; the destruction may be so extensive that very little blood-forming tissue remains.

The kidneys contain few parasites, which are carried there by the bloodstream. Those scanty parasites which have been found in the urine are probably derived from invasion of the bladder.

The lungs show no parasites, but are liable to secondary bacterial invasion on account of the leucopenia which is such a constant feature of this disease.

In the *gastro-intestinal tract* there is proliferation of reticulo-endothelial cells, especially in the duodenum and jejunum. The villi may become grossly hypertrophied and swollen by packed parasitized cells. Small ulcerations are not uncommon and parasites can be demonstrated in them.

The lymphatic glands are generally enlarged and congested, especially the mesenteric group, and the tissue is usually invaded by large numbers of leishmania. There is also hypertrophy of the retro-pharyngeal lymphoid tissue, and Leishman bodies can be found in nasal and pharyngeal secretions.

The underlying essential pathology of this disease is blockage of the endothelial system (Hu and Cash). The parasites are engulfed by the endothelial cells; they then multiply until the cell ruptures and the organisms, escaping into the bloodstream, are transported to other organs.

In acute outbreaks of kala-azar in new areas and in non-immune populations, as for instance, in N. Kenya, Clinton Manson-Bahr (1957) has found the parasites widespread, lying freely in the skin. They are also present in the internal organs, in the ventricles, suprarenals, parotid gland as well as in the liver and spleen. In this acute state they have not been demonstrated in the blood. This distribution accounts for the acuteness of the disease and resistance to treatment.

Symptoms.—The *incubation period* is difficult to fix. In one Englishman under Manson's care the time that elapsed from his arrival in perfect health in the endemic region and the onset of fever which terminated in kala-azar (diagnosed microscopically both before and after death) was under ten days. Kirk, on the other hand, from accurate observations in the Sudan, fixes the period between three and six months, but it may be as long as two years (Sweeney, 1945). Jopling (1955) has reported two with incubation periods of $2\frac{1}{2}$ and $1\frac{1}{2}$ years respectively and McRobert another of even longer duration, while a 9 year interval elapsed between the development of the disease in a Polish soldier and his arrival in England from an endemic area in Italy. In some artificially-infected dogs, the disease, like dermal leishmaniasis, may remain latent for months.

A primary lesion in the form of one or more minute dark red papules on the face was described by Mirzozian in Central Asia, and more massive ones on the legs occur in N. Kenya.

The onset may be gradual or sudden; if gradual, it cannot be diagnosed at all on clinical grounds. If sudden, there is usually high fever, which may be preceded by rigor and, in some cases, by vomiting. The initial fever may be very severe (Charts 6, 7). It is intermittent in some instances, more frequently remittent, often with a double remission in the twenty-four hours, resembling that of subtertian malaria. It lasts from two to six weeks, occasionally longer. Waves of fever, separated by apyrexial periods, may often simulate undulant fever, and during the pyrexial periods both the liver and the spleen enlarge. There may be daily rigors, so that

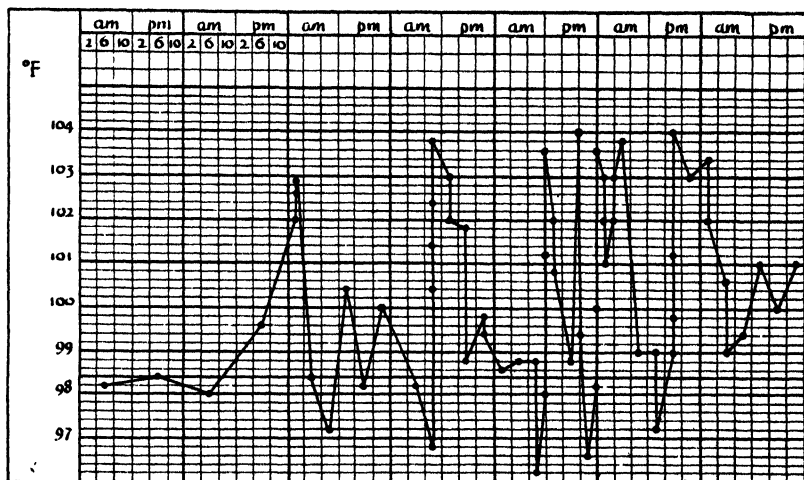


Chart 7.—Temperature chart of acute kala-azar, showing "double crisis."
(Dr. G. Carmichael Low.)

malaria may be suspected. A four-hourly temperature chart in a well-marked case may show a double or even a triple rise of fever.

It is now generally accepted that, though the underlying clinical picture is basically the same, there exist different clinical types and that the leishmania parasites vary considerably in virulence and in resistance to treatment. The Indian and Eastern forms are on the whole less deadly than the Sudanese or that encountered during the war in Southern Abyssinia and in Northern Kenya. The infantile Mediterranean form also appears to be a distinct clinical entity. Rarely the full clinical picture may not be developed. In soldiers who contracted the infection in North Africa and Sicily in 1943 some showed enlargement of the lymphatic glands, particularly of the cervical group, associated with complete freedom from other signs and symptoms. On the other hand, some of the Southern Abyssinian cases were extremely severe. A nodular rash developed which coalesced to form warty masses in which parasites were demonstrated.

LEISHMANIASIS

Geographical forms of kala-azar.—As our intimate knowledge of visceral leishmaniasis has increased, so it has become apparent that different types exist, which vary considerably in clinical symptoms, severity and response to antimony treatment. It can be suggested that these variations have come about as the disease has developed from its primitive state as a zoonosis. These differences can be set forth as follows:

I. Indian kala-azar.—The spleen is usually enlarged from the commencement of the illness, whilst the liver does not become appreciably bigger until the disease has lasted some months, but in rare cases in the initial stages, enlargement of the spleen may not be an outstanding feature. Hepatomegaly may persist for some months before the spleen becomes palpable. Generalized lymphadenitis is common, cervical adenitis may sometimes occur, and occasionally, too, there is enlargement of the epitrochlear glands.



Fig. 25.—Kala-azar in Indian boy. (Col. L. E. Napier.)

Then comes a period of apyrexia and general improvement, to be followed once more by fever, splenic and hepatic enlargement, and perhaps tenderness. In women amenorrhoea is often an early symptom. In this way spells of fever and apyrexia recur for months, until finally a low form of fever, rarely over 102° F. becomes more or less persistent. Profuse sweats are common during remissions at all stages of the fever; in the more chronic rigors occur exceptionally. Pains in the limbs often suggest rheumatism. When the disease is thoroughly established, emaciation and anæmia become noticeable, and, together with the enlargement of the liver and spleen, produce a typical appearance. Oedema of the legs, sometimes circumscribed, may be present. In many cases the skin acquires a strange earthy-grey colour; this dusky pigmentation, which has given rise to the native name, kala-azar, "the black disease," is best seen on the feet, hands and abdomen in Europeans, though very difficult to distinguish in dark-skinned natives. Das Gupta and colleagues (1954) have made a point that is often missed, that Indian patients who are often very emaciated show deficiencies of vitamins A, B and C, and treatment should be based on this assumption. The hair is apt to become dull, dry, and brittle, and may fall out:

petechiæ, in the axillæ especially, are not unusual; epistaxis and bleeding from the gums are common. This condition of chronic fever, enlargement of spleen and liver, emaciation, and anæmia may continue for months or even one or two years, until improvement sets in. More usually—96 per cent. of cases (Rogers), 150 recoveries in 2,000 cases (Price), 24

recoveries in 100 cases (Lignos)—the patient is cut off by some intercurrent disease, especially dysentery.

One outstanding clinical feature is that, in spite of the patient's weak, emaciated condition, the pyrexia, and the protuberant abdomen due to splenic enlargement, he preserves a good appetite and a clean tongue; he may be working with a temperature of 102° F. quite unaware that he has fever (Fig. 25). There is no malaise or apathy. In this respect kala-azar differs from malaria and other toxic fevers, such as typhoid. Kala-azar usually lasts several years, but the Sudan cases, especially, may run an acute course in about five months. In the terminal stages ascites may develop, due to gradually increasing cirrhosis of the liver. Anæmia may become progressively severe. Hæmic murmurs of the heart are often heard. Hæmorrhages may occur from any part of the body, and purpuric patches may appear on the skin after local injury. Death may ensue from several causes. When due to the disease alone it results from exhaustion. Dysenteric symptoms are frequent, and may be due to intestinal lesions caused by Leishman-Donovan bodies, or to a superadded infection with amœbic or bacillary dysentery. Bronchopneumonia and noma are frequent terminal symptoms.

Blood changes.—*Anæmia* is invariable in advanced cases and is due to destruction of the erythroblastic tissue of the bone marrow. These changes are not so obvious in the infantile form. The red blood corpuscles are often reduced to 2,500,000 per cu. mm. with a corresponding and parallel fall in hæmoglobin.

The most remarkable change is *leucopenia*. The leucocytes are reduced below 3,000 per c.mm. in 95 per cent. of cases; below 2,000 in 78 per cent.; and 1,000 in 42 per cent. The proportion of leucocytes to erythrocytes, normally 1 to 750, stands at 1 to 1,500 or even 1 to 2,000. The differential count usually shows a relative increase of lymphocytes, a moderate increase of large mononuclears and almost complete absence of eosinophiles. (The biochemistry of the blood is described on p. 149.) The liability of kala-azar patients to pneumonia and superadded septic infections is ascribed to leucopenia.

The reduction in leucocytes may proceed to acute *agranulocytosis*.

II. Acute toxic kala-azar.—When kala-azar breaks out in a new area, especially in the stress of war, it may assume an acute and almost unrecognizable form. This happened in Nigerian regiments in E. Africa during the 1940–41 Abyssinian campaign, as reported by Cole, Cosgrave and Robinson. The case mortality-rate of one outbreak was almost 50 per cent. The onset was sudden, often with rigors, headache, epistaxis, high fever, abdominal pain, vomiting, painful liver and spleen. In a proportion of cases the course of the disease was so rapid that the spleen never became palpable. Renal symptoms were noted, whilst the urine contained albumin and casts. The complications were hæmorrhagic: bleeding from gums, skin petechiæ, and blood-and-mucous stools. (Œdema was noted in three cases, and in three there was general anasarca (Cole 1944).)

III. Infantile or Mediterranean kala-azar.—This occurs typically in Malta where it has been graphically described by Debono. The youngest case was 4 months old, in the majority the age is 1–2. There are important bone-marrow changes in which the hæmopoietic elements are crowded out by proliferating endothelium, but the myeloblastic tissues suffer to an even greater extent, so that leucopenia is always a prominent feature and agranulocytosis is apt to supervene. This is responsible for the great liability to secondary infections and cancrum oris. The blood platelets are reduced to 100,000, so that thrombocytopenia results in hæmorrhagic purpura and ecchymoses. The incubation period is usually three to four months. In children under two the onset is acute with hyperpyrexia and vomiting. Untreated it is invariably fatal. In older children it runs a subacute course lasting six to eighteen months. The course of the disease may be cut short by bronchopneumonia or cancrum oris. Sudden death may be due to hyperpyrexia, vomiting, intense dyspnoea or hæmorrhage. A double crisis is common, one at 11 a.m. and the second during the evening, followed by sweating in the early hours of the morning. Fair children develop pallor rapidly with slight generalized œdema suggesting subacute nephritis. The lymphatic glands are usually enlarged. Splenic puncture is regarded as the most reliable test, but on account of the danger, blood culture performed with meticulous technique is preferable. The formol gel, antimony and other biochemical tests are not usually reliable before the fourth month of the illness. The clinical picture may resemble that of splenic anæmia (Banti's disease) very closely.

IV. Chinese kala-azar is distributed along the Yangtse river on the north bank to Peking. It occurs in the provinces of Chi-Li, Shan-Tung, Kiang-Su, Anhwei, Honan, Hu-Pei, as far south as Chiu Chiang and Hankow. The great majority of cases of splenomegaly in these parts are kala-azar. The oldest patients are about 50; the youngest about 2. Although the majority are found in the first three decades, it is not considered to belong to the infantile form. In general, according to Wylie (1920), the main symptoms do not differ from those elsewhere, but distinctive features are enlargement of the posterior cervical glands to the size of an almond which, on excision, contain leishmania.

V. Russian kala-azar has become prominent as it represents a zoonosis in its primitive stage. According to Latyshev, Kryukova and Povalishina, this leishmaniasis is prevalent in the subtropical regions of the Soviet Union. Since 1933 sporadic outbreaks have been reported, in increasing numbers, in Tadzhikistan during the reclamation of the Vakhsh (Bokhara) Valley. There the jackals (*Canis (Thous) aureus*) were found to be the reservoir of the infection. When this region was opened up human beings were brought into contact with these animals. This explains the peculiar features of visceral leishmaniasis in the rural districts of Middle Asia and Caucasus where the area of distribution is extensive, but incidence is low. The disease behaves like a typical zoonosis. In the densely populated towns of Middle Asia the situation is different for there visceral leishmaniasis has long ago adapted itself to man as the

principal host whilst retaining its infectivity for dogs who originally acquired the infection from jackals. In the rural districts of Middle Asia the highest incidence is in adults, whereas in urban areas 95 per cent. of cases are in children, possibly because of their greater susceptibility. The vector is *Phlebotomus arpaklensis*.

VI. Sudanese and E. African kala-azar.—In Kenya the was recognized, on clinical grounds, in 1927 and proved correct in the Elgeyo Reserve in 1984. From that time onwards, apart from an outbreak on the southern borders of Abyssinia in 1941, kala-azar was almost unknown till later in that year it began to spread in N. Kenya with great suddenness at Saricho in the Uaso Ngiro river in the North Province and subsequently at Nyomeni and Tseikuru, between Kitui and the Tana river, and in the Machakos District, apparently connected with a similar outbreak at Darbarruk in British Somaliland. In the suddenness of onset and rapidity of course it resembles the S. Sudanese form. There have been 3,000 cases in the Kitui district in the epidemic which has continued since 1946 (Heisch 1954).

The present outbreak commenced in October, 1952, and reached its peak in June, 1953. The age distribution is much the same as in the Indian form (C. Manson-Bahr and Heisch 1956). More than 57 per cent. are in the 4–18 age group. Epidemiological considerations are important. Termite hills of great height abound with ventilation shafts, 3–5 ins. in diameter, teeming with sandflies (17 species of *Phlebotomus* have been recognized of which 6 are new). Most feed on lizards. According to the presence of leptomonads in the pharynx suspicion has fallen on *P. garnhami* and *Sergentomyia* (a new genus) sp. nov. 2.

These termitaries are colonized by mongooses, spiny mice, geckos and also by gerbilles (*Diopodillus* and *Tatera*). These latter are reservoirs and absolute proof has now been obtained by the passage of *L. donovani* to man by inoculating gerbille and ground-squirrel blood into golden hamsters—from them to human volunteers (Heisch 1958). The special gerbille is *Tatera vicina* and *Exerus erythropus*, ground-squirrel. Dogs and jackals are not infected.

The disease in Kitui is less severe than that further north. Enlargement of lymphatic glands is common and general, though not larger than that of peas as in the Sudanese type. Parasites have only been found once in the peripheral blood. Associated skin lesions are of two types—small circumscribed lesions and later ones known as leishmanoid. The former are situated on the lower part of the legs and are irregular, hyperpigmented, circular areas 0.5–0.6 cm. in diameter with central depigmented scar and usually contain leishmania. They represent healed, primary “chancres” following bites of infected sandflies. The evidence is that they are caused by anthrophilic sandflies feeding on the legs of goatherd boys as they stand on anthills to guard their flocks. From this primary lesion leishmania spread to the inguinal glands and eventually, after several months, the complete syndrome of kala-azar supervenes. Post-kala-azar dermal leishmanoid was observed nine times. Toxic cases with bleeding from mucous membranes occur and usually have marked albu-

minuria. The leishmania are widely distributed on the skin. Response to treatment with antimony and pentamidine is disappointing (as in the Sudanese form) and there is great tendency to relapse. Urea stibamine has consistently given the best results.

The Sudanese form was studied 50 years ago by Balfour, Christopherson and Bousfield. In 1937 Archibald and Mansour described its epidemiology in the Fung district near the Abyssinian border west of the Blue Nile and in the Kapoeta district on the Uganda border. In this form, too, leishmania are widely distributed throughout the body and on the skin. The disease occurs mostly in adults. Although Kirk (1939) thought that some reservoir host must exist, so far none has been found. As in Kenya the action of antimony or pentamidine has been ineffective. The phlebotomus vector (Lewis and Kirk, 1954) appears to be *P. orientalis* or *P. clydei*. The following table illustrates the main differences between these different forms of kala-azar.

	INDIAN K.A.	SUDANESE K.A.	E. AFRICAN K.A.
Skin lesions with visceral disease.	Do not occur.	Fairly common on head and legs.	Sometimes seen on legs.
Frequency of leishmania in blood.	Often seen.	Rarely seen.	Rarely seen.
Response to pentavalent antimony treatment.	Good.	Little or none.	Little or none.
Incidence of relapse.	Not common.	Common.	Common.
Post kala-azar dermal leishmaniasis.	Latent period 1-2 years. Duration long. Found in 5-10 per cent. of cases.	Little or no latent period. Duration long. Found in 30 per cent. of cases.	Latent period 5-9 months. Duration? Found in a very small proportion of cases.

VII. S. American kala-azar.—There are remarkably few clinical descriptions of kala-azar in Brazil or elsewhere in South America. The type appears to conform more to the Mediterranean disease, except that there is a tendency to be associated with the skin manifestations of espundia (*L. braziliensis*) and which resemble those of oriental sore (*L. tropica*). There is no mention of glandular enlargement and most cases are amenable to trivalent antimony treatment as well as to the modern pentavalent compounds. It has been stated by Chagas and others that the reservoir hosts are dogs and cats, and in Brazil the South American foxes of the genus *Lycalopex* (*L. vetulus*) may also act in that capacity. In its epidemiology it has been remarked that South American kala-azar resembles that of the Sudan. The sandfly vectors are *Phlebotomus longipalpis* and *P. intermedius*. The first case was discovered by Migone in Paraguay in 1913. In 1926 two infantile cases were found by Mazza in Argentine children of 5 and 9; first one in Oran the second in Tabacal, both in immigrants from the Mediterranean. Penna, in 1934, reported that *L. donovani* had been found in the liver tissue removed by the viscerotome. Chagas found 70 cases in the Matto Grosso in 1938. Pons and Martinez in 1941 have

published an account of others discovered by the same method in the north Argentine.

Dermal leishmanoid.—A cutaneous form of leishmaniasis, in which the parasites occur in nodules in "butterfly patch" formation on face, forearms, inner aspects of thighs and pubic regions, was first reported by Christophers in India in 1904, and Thomson and Balfour in the Sudan



Fig. 26.—Dermal leishmanoid. Extensive nodular lesions on face and ears.
(Acton and Napier, *Ind. Jl. Med. Res.*)

in 1909, and has since been observed in the Blue Nile (Kassala) districts as well as in the recent epidemic of kala-azar in Kenya. It was described by Brahmachari in India under the name of "dermal leishmanoid," or "post-kala-azar leishmaniasis." No cases have been recorded in the Mediterranean and it is extremely rare in China. It is certainly a sequel to generalized infection with *L. donovani*, as more than half the patients who exhibit this curious eruption had suffered from kala-azar about one year previously and had been given antimony treatment. In Bengal 5 per cent.

of patients so treated have developed dermal leishmanoid. The leishmania are found in smears from the nodules, and cultures have been obtained from the lesions. It is not at all clear at present what the significance of this phenomenon is, or what factor causes the organisms to establish themselves in the skin. This condition occurs in all classes of the community, in persons of all ages and both sexes. Antimony appears to be specific, but cure is not so rapidly effected as in the visceral form. Stilbamidine is useless.

The first, or depigmented, stage usually appears as colourless patches on the face and upper extremities, gradually spreading to the remainder of the body. Minute dots gradually enlarge to irregular areas half an inch in diameter, which



Fig. 27.—Post Kala-azar depigmentation.

occasionally tend to break down. There is cedema of the subpapillary tissues accompanied by dilatation of the vessels. Below this there is infiltration by macrophages of the subpapillary plexus. The second, or nodular stage, is seen about two years after antimony treatment. (Figs. 26, 27.) Usually the nodules replace the depigmented patches, but there are certain areas, such as the face, where the nodules appear much earlier than in other parts of the body. They may extend to the mucous membranes and ears, and may closely resemble leprosy. In the Sudan a punctate cutaneous eruption has been described by Kirk, and in the larger nodules leishmania can be demonstrated, especially towards the completion of antimony treatment. The epithelium is thin and the subpapillary layer is cedematous, with atrophy of the fibrous and elastic tissue. Subjacent to this cedematous area is a granulomatous mass consisting of proliferating macrophages. There is also a xanthomatous form. These lesions are raised, orange-coloured plaques which are painless and do not ulcerate. The histopathology of leishmanoid has been described by Sen Gupta and Bharracharjee (1951). In the hypopigmented lesions changes in the epidermis are minimal, but in the erythematous lesions the changes are slight. In the nodular lesions the epidermis is thinned, flattened and reduced. Parasites are seen in all three types; they are easy to find in the erythematous, but are most numerous in the nodular lesions.

Preliminary treatment with massive doses of potassium iodide causes the nodules to ulcerate and they then become susceptible to intravenous injections of urea stibamine (see p. 151).

Association of kala-azar with oriental sore.—It was formerly considered that these two clinical entities were never associated, but this appears to be by no means invariable. Originally Christopherson, Kirk and Macdonald in the Sudan, described cases where visceral, cutaneous, and even mucosal lesions were present in the same individual. In China, too, Wang found subcutaneous nodules, composed of endothelial cells with many leishmania. In the Sudanese form of kala-azar circumscribed cutaneous ulcers with a tendency to coalesce are the most frequent.

In discussing the evolution of leishmania infections in man Kirk considers that no hard-and-fast line can be recognized between the three types. Leishmanoid nodules may resemble oriental sore. In one seen in London circumoral nodules were so small as to be mistaken for facial papillomata. They were recognized by their peculiar purplish colour, and they contained Leishman-Donovan bodies.

Eye lesions.—R. E. Wright showed that when eye lesions occur in kala-azar, as in malaria, they are due to retinal hæmorrhages in the posterior segment of the eye.

Immunity.—It has been shown that immunization against bacterial infection is not interfered with by the blockage of the reticulo-endothelial system which results from generalized leishmania infection.

Noguchi was able to demonstrate differences in antigenic structure between *L. donovani*, *tropica* and *braziliensis*, but that *L. infantum* and *L. donovani* were antigenetically identical. Some strains of *L. caninum* are closely related to *L. donovani*. Complement-fixation antibody was demonstrated by Hindle, using an emulsion of the flagellate stage as antigen.

Diagnosis.—Irregular chronic fever with enlargement of the spleen and diminution in the number of leucocytes in patients from the endemic zone suggests kala-azar. Examination of the blood can at once exclude leucocythæmia and also malaria, if taken together with absence of tertian or quartan periodicity and the inefficacy of quinine, atabrin or paludrine. Sometimes in early infections diagnosis is very difficult, when Leishman-Donovan bodies cannot be found, the formol-gel test is negative and eucopenia is absent.

Splenic puncture must not be lightly undertaken. A preliminary examination of the blood should always be made to ascertain the degree of anæmia, to exclude leucocythæmia and to obviate the necessity for splenic puncture, and the attendant risk of fatal hæmorrhage so easily induced in that disease. *Liver puncture.*—When the liver is enlarged, it should be punctured instead of the spleen as it is less vascular and less easily torn, but, as a general rule, the parasites are not so abundant and the results are therefore unsatisfactory. In performing puncture, the abdomen should be firmly fixed with a binder to prevent, as far as possible, movement of the diaphragm and consequent risk of tearing the punctured organ. The patient should be given sodium amytal gr. iii, or pethidine 100 mgm. per stone of body weight, one hour previously, and the puncture site infiltrated with novocain to deaden pain. It is wise to give vitamin K, 10 mgm. orally each

day for 3 days preceding puncture. The lower border of the spleen or liver should be steadied by the hand. A hypodermic needle, scrupulously clean and dry,¹ and connected with the barrel of the syringe by a short length of rubber tubing, should be used, the patient being directed not to start or breathe when the puncture is being made. The type of needle is most important. The bore should be neither too big nor too small. The Editor has found Maw's size No. 10, with a shaft 40 mm. in length, the most suitable, and Napier devised a special spleen-puncture syringe (Fig. 28). The patient should hold his breath in full inspiration whilst the needle is in the spleen. He should be given no food by the mouth for at least two hours before puncture. He should lie supine on the left side of the bed and the operator should stand on his left side. The skin is infiltrated with 2 per cent. procaine hydrochloride solution. Local anaesthesia is

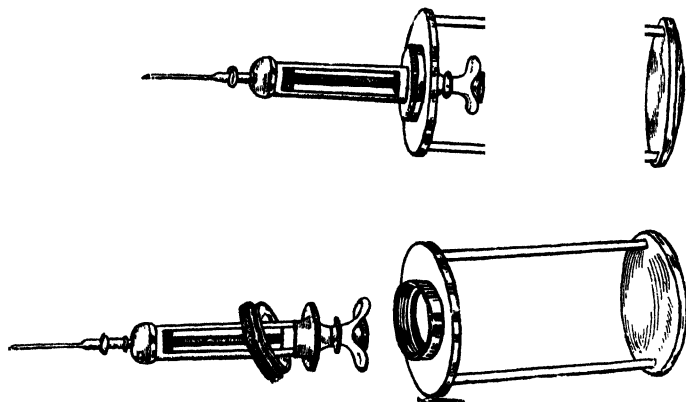


Fig. 28.—Spleen puncturing syringe. (After L. E. Napier.)

continued up to the peritoneal layer with 20 gauge needle. Failure to draw blood is not to be regarded as failure to obtain material for microscopical examination; on the contrary, it is an advantage, as the object is to procure spleen or liver pulp, not blood. After the contents of the needle have been blown out on a slide, it may be trans-illuminated by an electric pocket-torch to discover the minute sago-like masses of splenic tissue. A film should then be spread and, after it has dried, stained by Leishman's or Giesmsa's method, and then examined with a $\frac{1}{2}$ in. objective. Adler points out the desirability of culturing the material obtained on suitable media, as the parasites may be so few as to be missed by examination of smears.

Splenic puncture is not advisable in infants on account of the danger of laceration and intraperitoneal hæmorrhage. For puncturing the liver the site of election is the 7th or 8th intercostal space in the mammary line.

Liver biopsy is a very satisfactory method of demonstrating leishmania; it is far more efficient than mere liver aspiration with an ordinary needle and carries no greater risk than splenic puncture.

Lymphatic gland puncture is efficient and simple (Kirk and Sati), generally most efficacious in the glands of the groin and is similar to the method employed in trypanosomiasis (see p. 110).

Sternal puncture is safer than spleen puncture, and Chung in Peking considers it the best method, and that a local anæsthetic is seldom necessary. A shortened

¹ A trace of water in the needle will distort or burst the parasite and render it unrecognisable.

lumbar puncture needle is inserted at an angle of 30 or 40 degrees at the level of the second or third interspace. The needle, with contained stylet, is pushed with a boring action through the bony lamina. When the marrow is reached, the stylet is removed and a syringe for aspiration attached. Even in the absence of parasites, a myelogram is said to be distinctive. The average is: granulocytes 23, erythroblasts 24, hyaline leucocytes 53. Normally granulocytes are four times as numerous as erythroblasts and 3.5 times as hyaline leucocytes.

Blood examination.—The frequency with which this parasite has been found by blood examination varies in different localities. In some places, as in Madras and Assam, Leishman-Donovan bodies are evident in about 60 per cent. of all cases examined, enclosed within large mononuclear cells, and to a lesser extent within polymorphonuclear leucocytes.

Knowles and Das Gupta used thick films, prepared by placing four drops of blood on a slide, mixed so as to cover an area of $\frac{1}{4}$ sq. in. The film is covered with a Petri dish and dried at 37° C. for two hours. It is then flooded with glacial acetic acid (2.5 per cent.), 4 parts, crystalline tartaric acid (2 per cent.), 1 part, for five minutes. After tilting off the fluid, the film should be fixed with methyl alcohol and covered with dilute Giemsa stain. It is claimed that by this method leishmania can be found in 67 per cent. of cases.

Direct blood examination is very laborious and time-consuming. Blood culture or examination of gland, splenic or sternal smears are more practical.

The presence of the parasite in the peripheral blood can be verified by blood-culture. For this purpose 2 ml. of blood are drawn off by means of a 2-ml. syringe, and mingled with 1 ml. of 6 per cent. citrate solution in a sterile tube; this is placed in a cool incubator and allowed to sediment for two hours. The deposit is drawn up by a pipette, inoculated into two or more tubes of N.N.N. medium, and placed in a cool incubator. Examination of cultures is made about the tenth day, when flagellate forms are observed, but observation must be continued for at least twenty days. Splenic pulp may be cultured in the same manner.

Biochemical reactions.—The alkalinity of the blood is said to be decreased, while in some cases the coagulation-time is very considerably prolonged.

A specific *complement-fixation* test was introduced by Niyogi and Ray (1942). The antigen is prepared from washed flagellates from 48-hour cultures of *L. donovani*: 60 millions per ml. was found to be reliable. The suspensions were shaken for 48 hours in a machine and then kept in a refrigerator. A complement-fixation test with antigen prepared from the spleen of heavily-infected hamsters has been described by Weng and associates in China. This antigen can be dried and kept indefinitely in this state.

Aldehyde, "formol-gel test" (or the serum-formalin reaction (Brahmachari and Napier) proved to be very useful as a method of diagnosing kala-azar on a large scale. About 5 ml. of blood is withdrawn from a vein and allowed to stand a sufficient time for the serum to separate; 1 ml. of *clear* serum is then placed in a test-tube (3 by $\frac{1}{2}$ in.), and to this 1 drop of 30 per cent. formaldehyde, or commercial formalin, is added. The serum is at once well shaken and placed in a test-tube rack at room temperature. In a certain proportion of cases of kala-azar, especially in chronic cases, solidification of the serum takes place within a space of three to twenty minutes, but a control of normal serum should always be made. Napier himself states that "jellification" with opacity (like the white of

an egg) of the serum may be taken as diagnostic of kala-azar, if the disease is of more than three or four months' standing, but milkiness without solidification only takes place in early cases. But in exceptional cases even this reaction does not become apparent until an advanced stage. Should the serum be hæmoglobin-stained, this will change to chocolate-brown after twenty-four hours. In certain cases of syphilis, leprosy, hepatic cirrhosis, schistosomiasis, subacute endocarditis, lymphadenoma, phthisis, and malaria the serum will solidify, but remains clear and does not become opalescent as in kala-azar. The reaction, which occurs in twenty minutes, is given as +++; after two hours as ++, and after twenty-four hours as +, but an identical reaction is given by the serum of long-standing cases of trypanosomiasis.

For mass diagnosis Raghavan (1953) uses the following simplified technique. The blood drop is taken from the finger or ear into capillary tubes, 1 mm. in diameter, and 1 cm. in length. After the blood has clotted and the serum extends to $\frac{2}{3}$ the length of the tube, it is then stuck vertically on a base in plasticine and the blood cell permitted to sediment. Then the lower portion of the capillary tube, containing deposits of cells and plug of plasticine, is broken and discarded and the portion of fluid is brought into contact with 40 per cent. formalin or urea stibamine, and the liquid enters the tube by capillary attraction to a total of $\frac{2}{3}$ of the tube. Positive K.A. sera give a leucogel reaction in varying periods of time from a few minutes to 3 hours. The results are comparable with those obtained by Napier's method.

In kala-azar it has been proved that the plasma globulins are increased, while the albumins are diminished. In kala-azar, the albumins are 2.8; the globulins 4.0, as compared to 4.5 and 2.0 per cent. respectively in the normal. Lloyd and Powell constructed a typical globulin curve of kala-azar in which euglobulin constituted 40-50 per cent. of the total. Auto-agglutination of the red blood-corpuscles is often noted, as in trypanosomiasis, more especially in advanced cases. The thymol turbidity test of Rangue consists of the addition of 0.05 ml. of serum to 3 ml. of saturated solution of thymol buffered to pH 7.8. Readings are made with a Vernes photometer and a green screen after thirty minutes.

CHOPRA'S ANTIMONY TEST

This method is as follows: One to two drops of blood from the pricked finger are allowed to flow into a Dreyer's tube in which has been placed 0.25 ml. of a 2 per cent. potassium acetate solution. The tube is then inverted to mix the contents; a little of this mixture is transferred to another tube, and a 4 per cent. solution of the antimony compound (stiburea, for example) is added by means of a capillary pipette and allowed to percolate along the wall, so that it comes to lie below the blood mixture. In a positive case a flocculent precipitate forms at the junction. In very early cases it may not appear for 10-15 minutes: in the more advanced it is immediate. The character of the precipitate is important in kala-azar; it is so flocculent that it is not easily broken up by shaking, and it does not disappear in twenty-four hours.

In cases of doubt it is a good procedure to dilute the serum with 10 volumes of distilled water and to repeat the test. Alcohol must not be used for cleansing the finger. André (1932) claimed that the results are improved by reading the opalescence produced in kala-azar serum by urea stibamine by means of the "Vernes-Bricq-Yvon" photometer.

Napier stated that the aldehyde and antimony tests are almost of equal value. Out of 201 cases of kala-azar diagnosed by discovery of the parasite, 156 gave a positive antimony test, and 128 the aldehyde test.

Intradermal test (see p. 162).

¹ The Bramachari reaction or "ring test" consists of one part of patient's serum to two parts of distilled water when a ring forms. It is also non-specific.

The value of the "*leishmanin*" or Montenegro test, inoculated intradermally, as a reliable method of diagnosis is now being investigated. It is by no means so reliable as in oriental sore or espundia. It can, however, be stated that in Mediterranean and South American kala-azar it is negative but positive in Sudanese and Kenya kala-azar.

Differential diagnosis has to be made from splenic anæmia, bacterial endocarditis, cirrhosis of the liver and febrile reticuloses such as lymphadenoma sarcoidosis, trypanosomiasis, and Egyptian splenomegaly (*Schistosoma mansoni*) which, save for the absence of the parasite and the characteristic pyrexia, may closely simulate kala-azar. Visceral syphilis, with enlargement of liver and spleen, malignant disease and tuberculosis of the spleen, may have to be excluded. In China and Japan kala-azar may have to be differentiated from intestinal schistosomiasis (*Schistosoma japonicum*), in which enlargement of the abdominal organs may occur. The remarkably clean tongue and the good appetite serve in some measure to differentiate kala-azar from chronic malaria, to which may be added the considerable emaciation, absence of extreme anæmia, double daily rise of temperature (in 88 per cent. of cases), distension of the superficial abdominal veins, and pigmentation of the extremities.

TREATMENT

1. Treatment with pentavalent compounds of antimony.—

(a) *Neostibosan* is the amino salt of para-aminophenylstibinic acid, contains 40 per cent. of metallic antimony, and is comparatively non-toxic. It may be given in a strength of 25 per cent., either intravenously or intramuscularly. The doses may be given daily, but generally speaking, alternate days are preferable. The initial dose for an adult is 0.1 gm., the second 0.2 gm., the third 0.3 gm. This compound appears to be especially well tolerated. About ten injections are required for an average case, and a total of 2.7–4.0 gm. is usually necessary to effect a cure.

It has been pointed out by Neumann that in Malta, quite apart from the difficulties in administration, intravenous injections of antimony in children are apt to be followed by broncho-pneumonia, but neostibosan, when given intramuscularly, is almost equal in effect to the intravenous method. A dose of 2.5 gm. suffices within a period of six weeks. Debono, on the other hand, favours injection into the jugular vein in small children and considers the intramuscular method less satisfactory, and that by this method absorption is poor. The initial dose of neostibosan is 0.05 gm., increased by another 0.05 gm. (or 0.025 gm. in infants under one year) until limit of tolerance as shown by vomiting. The course is one of 16 injections. The average total dose is 0.1–0.15 gm. in babies under a year; 0.2–0.25 gm. under two years, and 0.3 gm. in older children. If after two months the spleen is still enlarged and Leishman-Donovan bodies present, a second course of higher dosage is advisable. Blood transfusions are necessary when the hæmoglobin is under 40 per cent. Penicillin has no effect on the Leishman-Donovan bodies, but is invaluable in treatment of intercurrent broncho-pneumonia.

(b) *Urea stibamine*,—*aminostiburea*, *carbo-stibamine*, *carbantine*—(stiburea— $C_6H_{11}O_6N_2Sb$), is a compound of urea with stibamine (*p*-aminophenylstibinic acid), and was introduced by Brahmachari. This compound is apt to undergo chemical changes if exposed to the air. Urea stibamine is undoubtedly an efficient preparation and often succeeds where other pentavalent salts fail; in resistant cases it may be given in combination with neostibosan; and the Editor

has seen successful results from this method. The total amount to effect a cure is about 3 gm., and the usual length of treatment is one month; if, for some reason or other, intermission in treatment takes place, the parasites tend to become antimony-fast. Urea stibamine may be given intramuscularly to infants in doses from 0.01–0.08 gm. in 1–2 ml. distilled water, a total of 0.65 gm. being necessary.

(c) *Solustibosan* 561 (pentavalent antimony gluconate) was introduced by Kikuth and H. Schmidt who considered it in many ways superior to neostibosan in the treatment of kala-azar. It is issued in ampoules of sterile isotonic neutral solution in water so that 1 ml. contains 20 mgm. of antimony; thus 6 ml. correspond to 0.39 gm. of neostibosan and contain 0.120 gm. of antimony. It can be given intramuscularly or intravenously. The initial dose is 6 ml. for sensitivity test. Thereafter it is 12 ml. daily, or on alternate days, up to a total of 120 ml. for an adult of 60 kg. weight. On account of the danger of allergic reactions it is advised that a break of ten days should be made between the fifth and sixth injections, if any untoward symptoms are observed. *Neostam* (B.W.) is a similar preparation. *Pentostam* (sodium antimony gluconate) has been used by Tuckman in Chinese kala-azar. The total dosage is 9 ml. for a child of 10 kg. and 30 ml. for adults of 50 kg. or over. This preparation is non-toxic.

Surmin (not to be confused with *Suramin*) is the name for the Russian brand of stibosan and solosuriamin is equivalent to solustibosan or sodium antimony gluconate.

Toxic effects of antimony treatment.—The “metallic taste in the mouth and throat need scarcely be considered as poisoning, but vomiting, giddiness, delirium, a considerable rise or fall in temperature, diarrhoea, and cramp in calves are to be taken seriously. They are danger signals and, when they occur, the injections should be temporarily suspended. Rapid pulse, cold, clammy skin, signs of collapse, in fact, are serious symptoms of poisoning.” Discomfort or pain in the chest, colic, headache, severe arthritic pains in shoulder and other joints, bone pains, especially in the shins, and even jaundice may be noted.

Disagreeable symptoms are less likely to ensue since the introduction of the pentavalent salts of antimony.

2. Diamidino stilbene (stilbamidine).—The Mediterranean, Kenya and Sudanese forms of kala-azar have proved more refractory to antimony treatment, requiring on an average double the amount necessary to cure the Indian strain.

Napier and his colleagues (1942) published results in a series of 100 Indian patients to whom stilbamidine was given intravenously in 1 per cent. solution. They concluded that the introduction of stilbamidine constituted a great advance in the treatment of kala-azar. Antimony-resistant cases responded particularly favourably. Weight for weight, only about one-quarter as much stilbamidine is required per case as neostibosan: 60 gm. suffices to cure 100 patients. The drug is apparently of no value in the treatment of dermal leishmanoid or cutaneous leishmaniasis.

It should be dissolved in 10 ml. of water and injected very slowly, otherwise it may cause vomiting. Administration is followed by a very considerable fall in blood pressure and also by a temporary decrease in blood sugar. The patient becomes flushed, with a burning sensation in chest and abdomen and slight dyspnoea, probably the result of stimulation of the parasympathetic system; these effects can be mitigated by adrenaline.

A disadvantage to the extensive application of stilbamidine has been the

supervention of neuropathies, sometimes as long as three months after the cessation of treatment, possibly from the action on the basal ganglia, producing anæsthesia of the head and neck. Napier reported that in half of his patients subjective disturbances of sensation ensued, such as hyperæsthesia, paræsthesia, anæsthesia, loss of sensation to light and touch, preservation of pressure sense and pain. In some these disturbances are transitory, in others they appear to be permanent. Epileptiform seizures have been reported by Kirk and Sati (1940).

Pentamidine isethionate (or *lomidine*) is now used in place of stilbamidine and does not produce such disagreeable after-effects. The doses are the same as employed for the treatment of trypanosomiasis (p. 115). The dose for adults is 180 mgm. on the first day increasing to 200 mgm. for 7–10 injections. Hazarika (1949) in 55 cases gave 10 per cent. solution of pentamidine intravenously in 25 and intramuscularly in 28; 10–20 injections were given and the total relative dose (per 100 lb. weight) ranged between 0·6 and 3·0 mgm. Vasomotor-symptoms constituted the side-effects. Ghosal and Sinha (1948) gave pentamidine intramuscularly on consecutive days in 10 per cent. solution: 1 ml. for the first, 1·5 ml. for the second and 2 ml. for subsequent doses. The temperature fell to normal after 5–6 injections.

Splenectomy in Kala-azar.—Nicolle and Compte in 1910 performed splenectomy in a dog, but it had no effect upon the course of the disease. In the same year, Alvares in Lisbon did splenectomy in a boy of 9. Though he recovered from the operation, he continued to harbour parasites in the liver. Similar results were obtained by Makkas in Athens, but in 1916 Kokoris reported the successful cure of a child of 3 in Greece. Cochran (1915), in the Chinese form, reported two successful cases in adults, and hæmorrhage was forestalled by the transfusion of 50–60 ml. of healthy blood. There was immediate marked increase of hæmoglobin and absence of leucopenia. Parasites were still present in the liver. In 1930 Timpano had a successful case in infantile kala-azar in Italy. Abrami (1931) also recorded a successful result in Mediterranean kala-azar in a woman of 35. A course of neostibosan and blood transfusion (200 ml.) followed the operation.

Martin, Chorine and Rouessé (1935) reported a similar case from the South of France.

Burchenal, Bowers and Haedicke (1947) have also recorded successful splenectomy in a negro soldier infected in North Africa. The formol-gel test became negative on the twelfth week after operation.

Prognosis.—Kala-azar is, in the great majority of cases, a chronic disease; but acute cases are noted in the early stages of an epidemic. Marked intestinal disturbance, ascites and liver cirrhosis indicate a bad prognosis, as does also extreme leucopenia. The prognosis is naturally affected by coincident infections such as malaria, the dysenteries and ancylostomiasis. Napier pointed out that with superadded pulmonary tuberculosis it is especially grave; but there is a tendency to spontaneous cure in about 10 per cent. of cases. The oft-repeated statement that, owing to the introduction of the antimony treatment, a 95-per-cent. mortality-rate has been converted to an equally high recovery-rate, is, therefore, not strictly true.

Prophylaxis.—Domestic and personal cleanliness is of great importance. Infected dogs should be destroyed, and in the endemic districts they should be kept away from association with man. Papantonakis proved that destruction of dogs in Canea in 1933 was followed by marked

decrease of kala-azar in the following year. Many years ago, by segregating the sick, burning houses, clothing and furniture, and providing new huts, Price, Rogers, and Young succeeded in banishing the disease in parts of Assam. Good results in prophylaxis have already followed the actual treatment of cases on a large scale. Energetic measures against sandflies should be instigated. This involves protection against sandfly bites and the control of sandfly breeding places by DDT residual spraying.

Prophylactic Inoculation.—Clinton Manson-Bahr (1959), in Kenya, has produced primary leishmaniomata in the skin of man by the inoculation of leptomonad cultures obtained from the gerbille, *Tatera vicina*, and a ground squirrel, *Ezerus erythropus*, as well as human cases of kala-azar.

These animal strains of leishmania are dermatropic, so that an artificial skin immunity can be produced by the inoculation of the ground squirrel strain without causing kala-azar. Further inoculation of human strains produced an arthus reaction at the site of inoculation and a similar reaction occurred in a cured case of kala-azar. It was suggested that the immunity in kala-azar is a skin immunity, as it is in oriental sore and therefore it should be possible to immunize a population against kala-azar by prophylactic inoculation of such an animal strain. After a successful "pilot scheme" mass inoculation of those exposed to infection is now being undertaken in N. Kenya.

II. ORIENTAL SORE

Synonyms. Tropical Sore; Bouton d'Orient; Delhi Boil; Cutaneous Leishmaniasis; Bouton de Biskra; Bouton de Bagdad; Aleppo Boil; Salek (Persia); Pendeh Sore (Southern Russia).

Definition.—A specific ulcerating granuloma of the skin, endemic within certain limited areas in many warm countries. It is caused by *Leishmania tropica*, and is characterized by an initial papule which, after scaling and crusting over, generally breaks down into a slowly extending and very indolent ulcer. Healing after many months, it leaves a depressed scar. The sore is inoculable and, usually, protective against recurrence.

Geographical and seasonal distribution.—In the French Sudan the distribution of oriental sore is co-extensive with that of *P. papatasi*. De Cisneros and Gomez state that cutaneous leishmaniasis occurs in association with kala-azar in Province of Murcia, S. Spain. Italy (Abruzzi and Teramo), Sicily, Crete, Cyprus, S. Spain. Cases have recently been reported from the French Midi and from the Pyrenees. Asia Minor—Syria (Aleppo), Palestine (Jericho), Red Sea Province, Egypt (Zagazig and Minia), Eritrea, Iraq (Baghdad), Caucasus, Arabia, Persia. India (Lahore, Multan, Delhi, Dera-Ismail-Khan, etc.). Transcaspia, Turkestan (Tashkent and Bokhara), China, especially Hunan. Sudan, N. Nigeria (Kano, Gusau, Katsina, Anzare), common N of 10° N. in Senegal and Darfur. In S. America it is often found, but not invariably, in association with espundia, especially in Peru, Bolivia, Brazil, Guianas, Mexico (Map III).

In the tropics it is especially prevalent about the beginning of the cool season: in more temperate climates, towards the end of summer or early autumn. Years of prevalence may be succeeded by years of comparative rarity—possibly in harmony with altered sanitary conditions. In Delhi, for example, in 1864, from 40 to 70 per cent. of the resident Europeans were affected with the local sore; when certain sanitary improvements were made, the frequency of the disease was immediately materially reduced.

Epidemiology and endemiology.—Although oriental sore may occur in countries where kala-azar is endemic, its distribution is as a rule quite distinct (see Map III). In India cutaneous leishmaniasis is confined to the west, whereas kala-azar is endemic on the east coast. In North Africa, oriental sore occurs north of latitude 35°, whereas kala-azar is found south of this line. In Persia and Iraq, where oriental sore is very common, kala-azar is rare. Central Asia is an exception for, according to Gerschenowitsch, they are found side by side, even in a single family, and both diseases have been seen in the same patient. Apparently also, recovery from cutaneous infection does not necessarily protect against subsequent infection by the kala-azar parasite. Oriental sore and kala-azar are found together in the Southern Sudan and also in Crete, where their respective carriers, *Phlebotomus sergenti* and *P. major*, are both present.

In the endemic areas oriental sore appears to have a seasonal preference, making its appearance in the dry season between September and January, in cities like Aleppo and Bagdad, where the disease is very common. In Turkmenistan the maximal incidence is æstivo-autumnal. Children usually acquire it between 2 and 8 years of age, and natives rarely attain maturity without having had one or more sores. In fact, it may be said that nearly every woman in Bagdad bears on her face marks of the ravages of this disease and for centuries it has been the custom there to inoculate children to prevent infection in later life.

Russian workers (Latyshev and Kriukova, 1942) in Turkmenistan recognize two nosologically independent types, and that the non-ulcerating form is the most typical. Kojevnikov's types are: *Leishmaniasis tarde exulcerans*, "dry type," and *Leishmaniasis cutanea cito exulcerans*, "moist type." The former is rural and is a zoonosis derived from animal reservoirs (gerbilles): the latter, urban, from human sources. Three types of foci are recognized which differ in their degree of contact with reservoir hosts. The *first* is in small settlements surrounded by desert which is inhabited by gerbilles representing a permanent source of human infection. The *second* is found in undeveloped settlements where gerbilles abound near human dwellings. Here the disease is endemic and there is a high incidence of oriental sores. The *third* occurs in large flourishing oases, whence the gerbilles have been forced to retreat, with the result that they are practically free from infection. Mountain foci are also known: one is at Kalai-Khumba (4,000 ft.), where the children are chiefly affected with multiple sores and the animal reservoir is absent. A somewhat similar association is found in N. E. Persia along the river Atrak, and, according to Ansari and Faghik, the moist form is common. Extracts

made from the ears of gerbilles (*R. opimus*), when inoculated into 3 humans, produced typical sores. A historical review is given by Pringle (1957), who has shown how the disease has spread from the Central Asian steppes to Iraq by adaptation to an antropophilic sandfly *P. sergenti* and finally to *P. papatasi* and directly spread from man to man.

Oriental sore occurs as a natural disease in dogs and cats. Canine kala-azar with cutaneous lesions has been found by Ho in Sian, China. The organism has been demonstrated in cutaneous sores on the ears, lips, nose and inner canthus of the eye of these animals in Teheran, Tashkent and Iraq, where it is only seen during the winter months (Machattie, Mills and Chadwick), recently in South America, India and in the Sudan, while Sinton has shown that the leishmania sores on the noses of dogs in India are transmissible to man. *Macaca* monkeys are also easily inoculated. Oriental sore has been found as a natural infection of the brown bear and bullock in Turkmenistan, and on the nose of a horse by Bennett in Kordofan. Natural infections in gerbilles (*Rhombomys opimus*) from Turkmenistan are common. Other gerbilles, *Meriones erythourus* and *M. meridianus*, and a "souslik," *Spermophilopsis leptodactylus*, have also been found naturally infected. The vectors are *Phlebotomus papatasi*, *P. arpaklensis* and *P. caucasicus* which breed in their burrows. An allied form (*L. myoxi*) occurs in the dormouse and *L. enriettii* is found in the guinea pig.

Ætiology.—The causative parasite—*Leishmania tropica*—is found in numbers in the granulating tissue at the edge of the lesion and may be demonstrated in scrapings. They frequently occur in rosettes, often enclosed in macrophage cells or in leucocytes. *L. tropica* resembles *L. donovani* in its morphology and behaviour, and in culture on N.N.N. medium. To collect material for cultivation the surface of a non-ulcerating sore is painted with iodine, and the edge is then punctured with a fine glass pipette. Like *L. donovani* the parasites grow best in the water of condensation. In heavy infections the flagellate, or *Leptomonas* forms, appear within forty-eight hours. Then the parasites undergo identically the same changes as do *L. donovani*, but they are able to flourish in conjunction with contaminating micrococci which the leishmania of kala-azar cannot do.

Noguchi once made the interesting observation that the addition of immune serum from an experimentally inoculated rabbit causes the organisms to develop in clumps.

In Syrian hamsters, and occasionally in mice, *L. tropica* produces generalized visceral leishmaniasis. Monkeys, dogs, mice and Syrian hamsters are experimentally inoculable, whilst donkeys, goats and sheep are refractory. In man a certain degree of immunity is produced so that, as a rule, second attacks of oriental sore do not occur.

Senekji and Beattie inoculated a large number of volunteers in Bagdad with cultural forms of *L. tropica*, and reproduced sores in the great majority. Subsequent attempts at reinoculation were unsuccessful.

There appears to be a close association between *L. tropica* and *L. infantum*. L. Brumpt (1958) has reported a singular instance where a

blood donor suffering from leishmanial warts on the hands and enlarged cervical gland conveyed the disease to an infant by blood transfusion, and it assumed the appearances of Mediterranean kala-azar. Bell, Carmichael and colleagues (1958), found in four servicemen from Malta, and Cyprus lymphadenopathy, at first confined to the neck, but subsequently spreading to axillæ and groins, was due to *L. infantum*. There were no constitutional symptoms; the main feature of the histology was the presence of giant cells, containing leishmania, and aggregations of macrophage cells.

Transmission.—Wenyon (1911) first suggested the sandfly (*Phlebotomus*) as the vector in Bagdad and found that 6 per cent. of these insects in Aleppo harboured a flagellate of the *Leptomonas* type in their intestines. Later, further confirmatory evidence was brought forward by the Sergeants, Parrot, Donatien, and Béguet (1921), who produced oriental sores in Algiers after scarifying the skin and applying a saline suspension of crushed *P. papatasi*. The incubation period was two and a half months. These sandflies were caught in Biskra, where oriental sore is common, and transported 600 kilometres to Algiers, where the disease does not occur. Later still, Adler and Theodor repeated these experiments with a *Herpetomonas* which is a natural infection of *P. papatasi*. The development of *L. tropica* in the body of the sandfly resembles that already described for *L. donovani*. Adler and Theodor have strikingly confirmed this, and have produced infection of *P. papatasi* by feeding these sandflies through a membrane on emulsions of leishmania. Thus Adler and Ber (1941) produced 28 sores in five volunteers by the bites of infected sandflies.

The vector in North Africa and the Eastern Mediterranean is *P. papatasi*; in Crete, Iraq, India and Persia *P. sergenti*. In Italy, according to Vanni, *P. perfiliewi* (*macedonicus*) is the chief carrier. In Central Asia the vectors are *P. caucasicus*, *P. papatasi* and *P. arpaklensis*.

Pathology.—There is continuous progression of cellular changes, so much so that a section taken at any particular time cannot give a complete picture of the processes involved. In the early stages there is proliferation consisting almost entirely of reticular cells, which form a syncytium. This proliferation may be so dense as to interfere with nutrition of the epidermis, whilst the proliferating reticulum is packed with parasites. Later, there is an invasion of lymphocytes, plasma cells and large mononuclears, and occasionally giant cells, accompanied by a considerable diminution of parasites. It may, therefore, be regarded as part of a protective mechanism, albeit not a very successful one, because the lesion, though now containing relatively few parasites, may still persist for months. Gradually, the lesion is replaced by scar tissue. In some cases parasites are very scanty in all stages, and, in these, there is a local infiltration of lymphocytes, plasma and giant cells. The histological, as well as the clinical picture may resemble lupus very closely.

Immunity.—A considerable degree of immunity is produced by repeated infection with oriental sore, which eventually becomes absolute—a fact which has been well recognized in Bagdad. On experimental grounds this was proved by Laveran, who found that repeated inoculation produced immunity in experimentally-infected dogs.

Firth (1912) and Berberian (1939–40) in reviewing the traditional practice of inoculating children with oriental sore try to ensure that the unsightly scar

should be in an inconspicuous site and there is no doubt that under these conditions, person-person infection can occur.

Incubation period.—The incubation period of oriental sore is variously stated in days, weeks, or months. That it may be a brief one, a few days or weeks, seems to be established by the appearance of the sore within a short time of arrival in endemic districts, or after inoculation. That it can be of much longer duration is equally certain. Manson saw an unquestionable oriental sore which did not appear until five months after the patient had been exposed to any possibility of

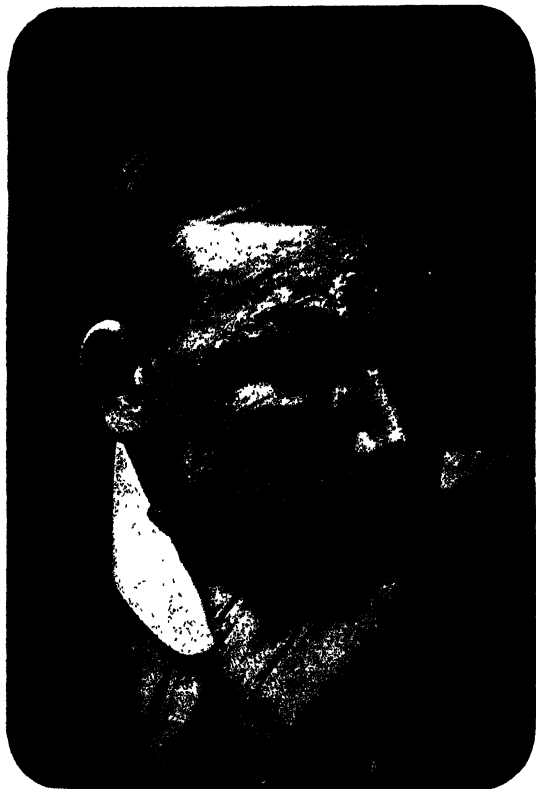


Fig. 29.—Oriental sore. (After Wenyon. Photo: R. McKay, reproduced in "*Journ. Lond. School Trop. Med.*")

infection. Senekji and Beattie (1940-1), in studying the development of experimentally produced oriental sores in man, found that the incubation period after infection of three million leptomonad forms from cultures of *L. tropica* ranged from 2 to 8 weeks. Wenyon inoculated himself with oriental sore in Aleppo, but it was not until six and a half months later that a leishmania-containing papule, subsequently developing into a sore,

appeared at the site of inoculation. In some cases the incubation period appears to be as much as fifteen months, or even as long as three years (Smith, 1956). Sometimes eruption of the sores is accompanied by fever and other constitutional symptoms, and temperatures up to 108° F. have occasionally been noted.

Symptoms.—The local lesion in oriental sore commences as a minute itching papule which tends to expand somewhat as a shotty, congested infiltration of the dermis (Fig. 29). After a few days or weeks the surface of the papule becomes covered with fine, papery scales. At first these scales are dry and white; later they are moister, thicker, browner, and adherent. In this way, a crust is formed which, on falling off, or on being scratched



Fig. 30.—Oriental sore on nose showing lymphatic spread to chin.
(By permission of Medical Department of the Navy.)

off, uncovers a shallow ulcer. The sore now slowly extends, discharging a scanty ichorous material; this from time to time may become inspissated, and a crust forms, while the sore continues to spread underneath. The ulcer extends by the erosion of its perpendicular, sharp-cut and jagged edge, which is surrounded by an areola of congestion. The centre portion contains a horny spicule, known as the rake or "Montpellier" sign. At the base of the lesion there is what is known as the "pearl sign" and which contains the leishmania parasites. Subsidiary sores may arise around the parent ulcer, into which they ultimately merge. These sores, usually about an inch in diameter, may come, in some instances, to occupy an area several inches across.

After a variable period, ranging from two or three to twelve or even more months, healing sets in. Granulation is slow and frequently

interrupted. Often it commences at the centre, while the ulcer may be still extending at the edge; often it is effected under a crust. Ultimately, a depressed white or pinkish cicatrix is formed. Contraction of the scar may cause considerable and unsightly deformity. Thus, on the face, scar tissue may produce retraction of the external canthus (epiphora) deformity of the naso-labial folds or eversion of the angle of the mouth.

Oriental sore may be single or multiple. Two or three sores are not uncommon; in rare instances as many as one hundred and fifty have been counted on the same patient. They are mostly situated on uncovered parts—hands, feet, arms, legs and, especially in young children, on the face; rarely on the trunk; never on the palms, soles, or hairy scalp. Occasionally these ulcers may occur on the ears, tip of the nose (Fig. 30), lower lip, and even on the tongue (Hawes, Panja, Dastidar, Trifilo), and three cases have been reported on the upper eyelids by Kamel in Cairo. These complications seem to be more frequent than had been supposed, and provide a link between the Old and New World leishmaniasis. A small multiple form may resemble diffuse papillomata: very rarely they occur on the buttocks or on the perineum. The Editor recorded a case in which a diffuse indurated swelling, resembling an oriental sore, close to the anus contained large numbers of *L. tropica*. An exceptional and rather similar case is related by W. St. C. Symmers (1960) in a married woman of 38 who developed an ulcer in the vagina which, after many vicissitudes, was found to be of leishmanial origin. She had never been out of the British Isles. There was no doubt that the infection was sexual. The husband was found to have contracted kala-azar during the war in the Sudan or Ethiopia in 1941. By 1944 he was pronounced cured, but the following year developed "leishmanoid" and was treated with pentamidine isethionate. He married in 1953 and his wife developed the ulcer two years later. Her spleen was enlarged and biopsy of an axillary lymph gland revealed *L. donovani* in abundance. No parasites were found in the urine, prostatic secretion or semen. This case raises once more the connection between kala-azar and oriental sore.

In a very few instances the initial papule does not proceed to ulceration, but persists as a scaling or scabbing, non-ulcerating, flattened plaque—just as sometimes happens in the primary sore of syphilis. Sometimes the ulcer is quite superficial, an erosion rather than an ulcer. Occasionally, from contamination with the organism of some other infectious acute inflammatory skin disease, the primary lesion may become complicated, and perhaps a source of serious danger. Otherwise, oriental sore is troublesome and unsightly, rather than painful or dangerous. When ulcerated, or secondarily infected, the neighbouring lymphatic glands in the area of the sore may be enlarged.

Associated subcutaneous nodules have frequently been described. Thus, Byron Evans (1938), in a case of extensive cutaneous leishmaniasis, found, around the arm lesions, five separate apple-jelly-like papules. Others were seen around similar lesions on the opposite arm or leg. In size they varied from 0.25 to 1 cm. in diameter; they were firm, discrete and freely movable and were not tender. On removal, they showed chronic inflammation with fibrosis, and Leishman-Donovan bodies,

suggesting a chronic lymphatic infection and denoting the spread of the infection *via* the lymphatic route. Lymphatic nodules were described as early as 1847 by Poggioli and by Bonne (1901), and also, in association with South American leishmaniasis, by Darier, de Christmas, Escomel and Werner.

In Christopherson's case (1928) there were twenty-five vesicular lumps of varying sizes which contained leishmania, while the Editor found similar swellings on the dorsum of the hand and over the submental gland in his patient. Gonzalez, Boggino and Rivarola described a similar case



Fig. 31.—Diffuse cutaneous leishmaniasis of foot in Ecuador.
(Dr. L. A. León, Quito.)

in 1937. A sharp bout of pyrexia (T. 103–104° F or 39.4°–40° C frequently precedes the appearance of the nodules.

Nodular or verrucose form.—A peculiar kind of dermal leishmaniasis, or parasitic granuloma, has been described by Ferguson and Richards in Egypt (Fig. 31) and by León in Ecuador. These lesions, which usually affect the lower extremities, resemble warty out-growths or papules; they may be solitary or multiple, and may be the result of auto-inoculation. They are best treated by excision.

Leishmaniasis recidiva.—The relapsing tuberculoid form, most frequent in Iraq and Anatolia, involving large areas of skin, especially of the face, is an allergic manifestation and therefore analogous to cutaneous tuberculides, closely resembling lupus vulgaris (Fig. 32).

It has been termed “metaleishmaniasis” by Marchionini. Some types resemble erysipelas with “serviette” distribution on the face.

Allergic manifestations are common on the nose and sometimes there

are blood-borne metastases resembling skin tuberculides. Chronic forms with dried and fissured scabs resemble tertiary syphilis.

Sometimes Leishman-Donovan bodies are very scanty in preparations, but they can usually be isolated by culture. Relapses occur after the original lesion heals and often take the form of nodules and papules, situated at the periphery of the scar and closely resemble "apple-jelly" nodules. Christopherson originally described them on the cheek, and also recognized a keloid form. Leishmaniasis recidiva is resistant to all forms of treatment except the Grenz rays.

Generalized non-ulcerating form (dermal leishmanoid).—Brahmachari described papillomatous nodules over the whole of the body, due to Leishman-Donovan bodies, which at first were thought to be tuberculoid leprosy (*see* p. 529), but all cases had previously been treated for kala-azar, and had apparently recovered after antimony injections.

Secondary infections.—Superadded staphylococcal or streptococcal infections are common. Secondary diphtheritic and streptothric infections have been described.

Diagnosis.—On clinical grounds these sores have to be distinguished from the desert or veld sore (p. 650), tertiary syphilis, *ulcus tropicum*, lupus vulgaris, and blastomycosis. The distribution of the sores and the presence of the Leishman-Donovan body render the diagnosis not a difficult matter. The parasites are best demonstrated by sterilizing the skin at the edge of the ulcer, and running in a fine glass pipette through a puncture made in the skin, to get beneath the ulcer, and obtain serum and tissue cells—but not blood—if possible free from bacterial contamination. This is a better method than scraping the surface of the ulcer with a blunt needle or with a fine knife. If parasites cannot be found, cultures should always be made. Additional help may be obtained by the *leishmanin*, or *Montenegro test*:

the intradermal injection of 0.1 ml. of a suspension of flagellates in culture (1,000,000 per ml.). A specific reaction is produced in active, as well as in healed, oriental sore lesions. Care must be taken to distinguish the Leishman-Donovan bodies from yeast cells, which are sometimes present in cutaneous ulcers and may closely simulate them.

The aldehyde test is negative.

In leishmaniasis recidiva differential diagnosis has to be made from tuberculides of the hypoderm, including Bazin's disease and also from syphilis. Adler insists that the apple-jelly nodules so closely resemble lupus that

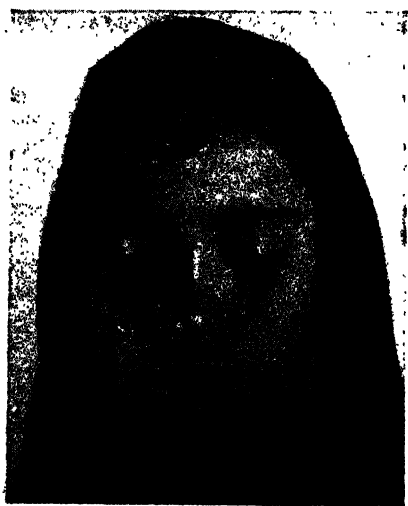


Fig. 32.—Cutaneous leishmaniasis in Egyptian girl. Lupus-like "apple-jelly" nodules. (Dr. H. K. Giffen, Assiut.)

cultures on NNN medium should always be made to grow the parasites (Fig. 32).

TREATMENT

The treatment of oriental sores in general, especially in a temperate climate, does not, as a rule, entail any particular difficulties, for the reaction of the tissues to the particularly indolent ulceration depends to some extent upon the general nutrition and environmental conditions. When the patient is removed from the endemic area, the disease tends to disappear spontaneously in about one year.

(a) **General measures.**—When the sores are multiple, as they so often are, and when they are situated on the extremities, undoubtedly the best treatment is intravenous injections of antimony, especially the pentavalent compounds (p. 151). Fouadin is the best trivalent compound given in 3-ml. doses on alternate days—three times weekly for 8–10 injections of the pentavalent. *Neostibosan* or *Neostam* are equally suitable and, when feasible, should be given intravenously in doses commencing with 0.1 grm. and increasing on alternate days to 0.3 and 0.4 grm. Much smaller total quantities (1–2 grm.) effect a cure than in kala-azar. For women and children, to whom injections cannot be given intravenously, the intramuscular route should be chosen (see p. 151). *Solustibosan* (p. 152), in oily solution intramuscularly for ten injections twice weekly, is praised by Marchionini in Turkey. Ball and Ryan found in 221 cases in American soldiers that *neostam* was most effective, intravenously, twice weekly, from 0.05 to 0.2 grm., with a total of 1.4 grm. The average time for cure was 14½ weeks. Raymond and Cruickshank, in an account of an epidemic of these sores following the Quetta earthquake, found injection of trivalent antimony compounds (tartar emetic and fouadin) combined with local scraping the most effective method. Pentavalent antimony preparations were less satisfactory under the conditions prevailing.

(b) **Local measures.**—Intravenous injections of antimony do not act so well for sores situated on the face—eyebrows, nose, cheeks, lips—and hands, which tend to be chronic, indurated, and subject to secondary infection.

Secondary infection is a most important element and in these cases no treatment is of any avail until the scabs have been removed and the sepsis cured by hot fomentations, eusol dressings, and nitrate of mercury ointment. Penicillin has been used with good effect by Marchionini, streptomycin and dihydrostreptomycin both by local infiltration and systematically has been used by Kochs (1954). 0.25–0.5 grm. in 1–4 ml. of water for infiltration and for systematic use 0.5 to 1.0 grm. daily up to 25 grm.

Ointments.—Various applications have been found useful on different occasions, e.g. *Cignolin* (a refined product of chrysophanic acid), in the following formula :

R	Cignolin	gr. iv (0.259 grm.)
	Ichthyol	gr. viii (0.518 grm.)
	Ol. cadini	℥ xl (2.368 ml.)
	Benzol rect. ad	℥i (28.42 ml.)

Ft. pigmentum : To be applied to sore every day.

This paint should be applied to the sore with a camel-hair brush, care being taken not to overlap on to the surrounding skin, daily for 2-4 weeks, after the sores have been cleaned up with eusol dressings or boric fomentations. This treatment is especially applicable to sores on the face in children.

Other ointments which have been recommended are : *Pellidol* (Bayer), containing 2 per cent. diacetylamine-azol-toluol, *Desitin* (Klinke) (chlorine and cod-liver-oil salve), and *Orisol* ointment, which contains berberine sulphate. Good results have been reported from the local application of phosphorated oil, and also from finely-powdered permanganate of potash.

Injections into the base of the sores.—Good results are reported by Flarer (1938) and Marchionini (1948) by infiltrating the surrounding skin with solutions of atabrin in 15 per cent. solution, especially in the early stages. Berberian tested this treatment on six cases, artificially produced by cultures of *L. tropica*, with 1-2 ml. of 10 per cent. solution.

Treatment of indolent sores on the nose.—These require special mention as, on account of the induration of the surrounding tissues, they are especially refractory and they do not appear to respond to the applications which are efficacious in other situations. After being cleansed, the bases should be scraped by a Volkmann's spoon and dilute nitrate of mercury ointment thoroughly rubbed in. Dry dressings and sulphonamide paste should subsequently be applied and pentavalent antimony injected intravenously.

Prophylaxis.—In the endemic areas insect repellents (*see p. 91*) should be used to protect the exposed parts against bites of *Phlebotomus*. Breeding places of this insect should be abolished. In Turkey, for instance, the local practice of plastering walls and sheds with cowdung which forms an ideal breeding medium for phlebotomus larvae should be prohibited. At night-time a fine-mesh netting, forty-five holes to the square inch, is necessary to exclude these insects (*see Fig. 12*). Dogs with suspicious-looking sores should not be permitted near dwellings. Prophylactic inoculation with cultures of *Leishmania tropica*, in the flagellate stage, has been practised in south-east Russia (Lawrow and Dubowskoj). Sores develop at the site of inoculation after an incubation period of two to six months. The immunity thus produced protects against further infection. Berberian states that, after inoculation of infective material, immunity takes 240 days to develop. This occurs when the papule ulcerates and commences to heal. Katzenellenbogen vaccinated 416 people in Palestine. In 45 a febrile allergic reaction developed. This inoculation campaign eventually produced favourable results.

III. LEISHMANIASIS AMERICANA

Synonyms. Espundia ; Bubas Braziliانا ; Uta ; Pian Bois ; Forest Yaws (British Guiana) ; Bosch Yaws ; Naso-pharyngeal Leishmaniasis ; Bay Sore (Honduras).

Geographical distribution and epidemiology.—South and Central America from Peninsula of Yucatan 21° N. latitude 30° S. in Argentine.

Prevalent in N. Argentine and Paraguay at 25° S. Brazil, São Paulo, Bahia, Rio de Janeiro (residential quarter), Peru between 5° and 25° South. British Honduras, Honduras, Martinique, Guatemala, Colombia, Costa Rica (Garcia), British, Dutch and French Guianas, Uruguay, Bolivia, Ecuador and Mexico (Campeche) (Map IV).

Occasionally, somewhat similar clinical cases have been reported from the Sudan (Christopherson, Humphreys, Mayne and Kirk), Somaliland, Italy and Kenya (Piers, 1947), India and China.

Mutilations of the face, reminiscent of this disease, have been found in figures engraved on old Inca pottery. Endemic zones in Brazil are known to the inhabitants as "Tapir nose" country (Figs. 33, 34).

It is prevalent in the northern part of Argentina and in Paraguay at 25° South. Altitude is a limiting factor. Most of the territory has an elevation of less than 2,000 feet. Heat and moisture are necessary for its existence. In the chicle (gum) forests of Yucatan the infection is contracted during the rainy season.

In highly endemic areas the majority of cases occur after six months residence, especially in the autumn. The prevalence of disease is definitely related to the density of the sandflies which transmit it.

In Paraguay the disease has assumed epidemic characters, and a large proportion of the population in certain districts, and 70-80 per cent. of prospecting parties, have become affected, so that most drastic public measures have had to be taken to prevent its spread. It is usually seen in men working in the forests, especially gum-pickers. A similar disease has been observed in the dog in the endemic centres, and it is possible that it occurs in the agouti (*Dasyprocta aguti*). Workers in the Gorgas Memorial Laboratory (1957-8) have demonstrated the presence of leishmania in the spiny rat (*Proechimys semispinosus*), though they could only be demonstrated by culture. Kirk has produced espundia in a monkey, *Cercopithecus aethiops*, in the Sudan, infected experimentally with Sudanese kala-azar (1946). Amongst all the numerous animals thus infected this is the only one in which the oro-nasal lesions of espundia have been observed. Pestana, Villela and co-workers working on the epidemiology of this disease in São Paulo, Brazil, concluded that intimate contact with wooded country is not always necessary. It is usually rural in distribution, but has been seen in some towns. Garcia thinks that in

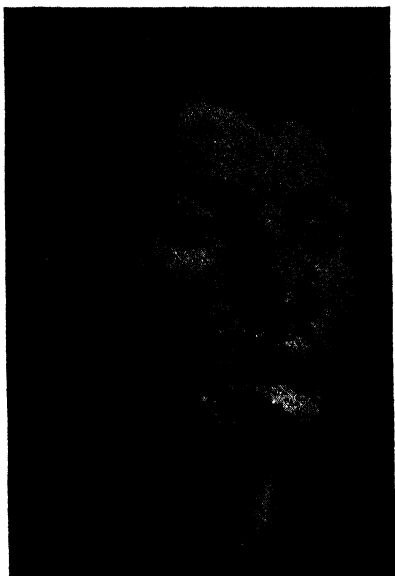


Fig. 33.—Espundia from Ecuador (Tapir Nose). (Dr. L. A. León, Quito.)

Colombia the dog is the reservoir of infection. The duration of the disease is from four months to four years. In the majority there are mixed mucosal and cutaneous lesions.

Etiology and symptoms.—The disease occurs at any age in either sex, in strangers as well as in the indigenous population. São Paulo seems to be an exception, as Villela says it is there nine times more common in men than in women. It begins as a sore on some mucous surface, of the chancrous form of the ordinary oriental-sore type. It heals in time,

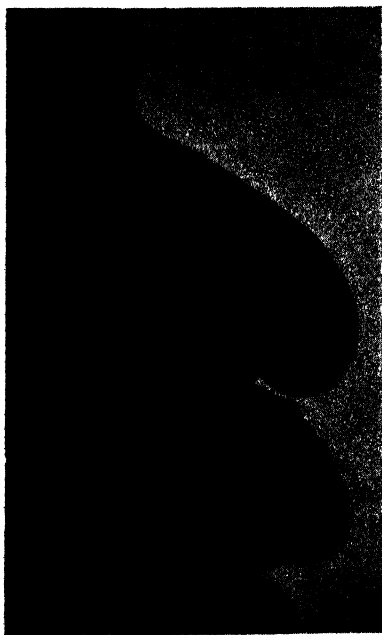


Fig. 34. S. American leishmaniasis
"Tapir Nose". (Dr. L. A. León,
Quito).

leaving a characteristic scar. Lesions on the nose causing great deformities are common and in the atrophic form they are characterized by a dry mucosa and the formation of crusts which impede respiration. Laryngeal lesions cause hoarseness, cough, dysphagia or dyspnoea. After an interval of months or years, most intractable fungating and eroding ulcers (Fig. 38) break out on the tongue, and in the buccal and nasal cavities, destroying and obstructing them, and ultimately, if untreated, leading to death by exhaustion after years of suffering. The lymphatic glands are often involved, but the abdominal and thoracic organs are spared. Though affecting the mucous membranes in this characteristic manner in the endemic zones, ulcers, as in oriental sore, occur in other uncovered parts of the body (Fig. 35). They have been commonly noted, mostly in men, as lupus-like lesions on the pinna of the ear in gumpickers (*oreja de chichleros*) (Fig. 36), known as "Bay sores" in Honduras. For the State

of São Paulo, Brumpt and Pedroso record localization of sores as follows (in percentages): Leg 30, foot 12, forearm 12, head 11, hand 10, hip 4, elbow 4, trunk 3, nasal mucosa 3, knee 2, buccal mucosa 2, neck 2, arm 1, pubes 1. These ulcers on the legs are distinguished from tropical ulcers by their painlessness. On the other hand Forattini and colleagues have found cutaneous lesions only, resembling oriental sore on the arms and legs in the territory of Amapá, Amazonia, Brazil.

Leishman bodies are found, though not in great profusion, in scrapings and sections of the fungating ulcers, and present no morphological differences from *L. tropica* or *L. donovani*, but have been separated on

serological grounds by Vianna as *Leishmania braziliensis*. Biaji in Mexico wishes to call the form confined to S. E. Mexico, *L. tropica mexicana*. The parasites can be cultivated in the same manner as *L. tropica* and on the same media, but Geiman showed that *L. braziliensis*, grown on the chorio-allantoic membrane of the chick embryo, shows much poorer infectivity than *L. tropica*. The histological picture consists mostly of epithelial proliferation and granulations with dense infiltration of round cells, plasma cells and, quite frequently, Langhan's giant cells which are distributed irregularly through the tissues. It is believed that the original sore in this grave form of leishmaniasis develops at the site of the bite of a jungle insect, probably a sandfly—*Phlebotomus*—and the following species are suspected (Shattuck, 1935): *P. squamipes* (Dutch Guiana and Brazil):

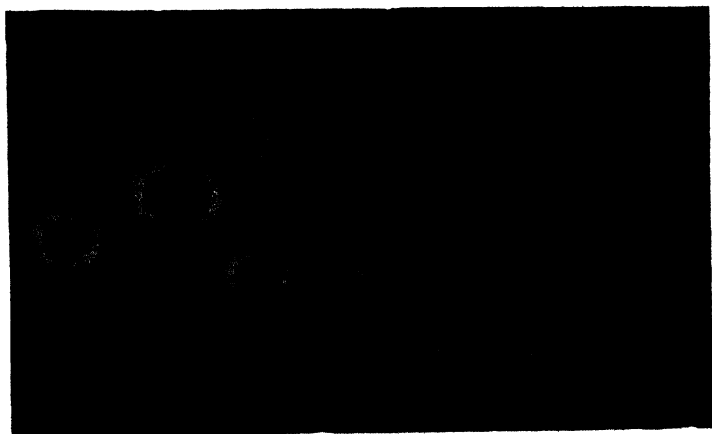


Fig. 35.—Punched-out ulcers in dermal leishmaniasis associated with Espundia in Ecuador. (Dr. L. A. León, Quito.)

P. intermedius (Brazil and Argentina) ; *P. migonei* (Venezuela, Brazil, Paraguay and Argentina).

These sores infiltrate deeply into the tissues, and, besides grave destruction of the nose, lips, and tongue, they may be followed by secondary infections, such as erysipelas and even gangrene.

Diagnosis is made upon the typical clinical appearances and the discovery of the parasite. Espundia has to be distinguished from ulcerating yaws (gangosa), lupus, leprosy and syphilis. In ulcerated lesions the crust should be removed and smears made from the underlying seropurulent discharge.

The excision of a piece of granulation tissue and the expression of the contained serum on a slide often afford a more ready diagnosis. In five cases discovered in the Sudan, Humphreys and Mayne found the leishmania in material obtained by pinching the lobulated growths, but not by splenic

puncture. The intradermal (*leishmanin*) test of Montenegro is usually positive and consists of an extract of flagellates (on culture) washed in physiological saline solution containing 0.4 per cent. phenol. This can be kept for long periods in the ice-chest. Gomes found it was moderately positive in 97.5 per cent. of South American cutaneous leishmaniasis. *L. enriettii* of the guineapig which can easily be cultured, can be used for antigens for the Montenegro test (Echandi).

The exact relationship of the mucosal leishmaniasis in the Sudan to espundia is not easy to determine. The South American disease has a

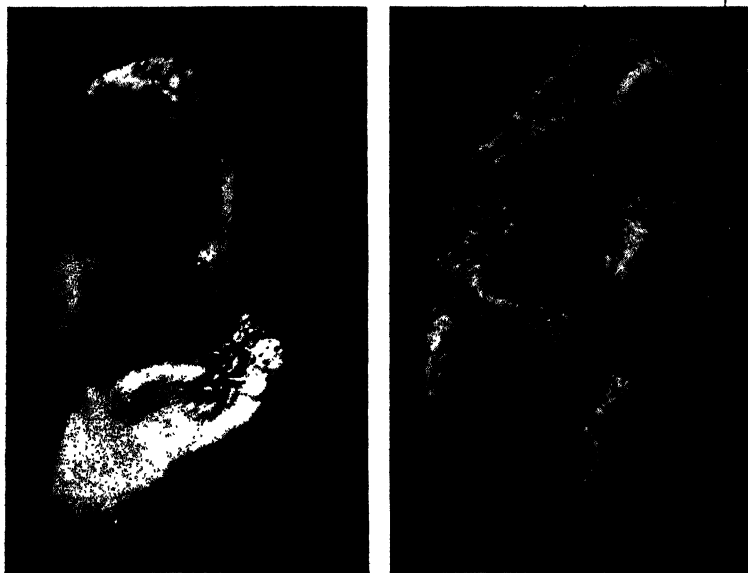


Fig. 36—S. American leishmaniasis of pinna of ear, "Oreja de Chichleros."
(Dr. L. A. León, Quito.)

specific course of evolution and occurs in epidemic form, which is not the case in the Sudan, where naso-pharyngeal leishmaniasis is relatively uncommon. In the nose the nasal septum and alæ nasi may be involved, whilst localized swellings occur on the lower lip. In almost every instance there, evidence of a concomitant visceral infection has been noted.

Treatment.—The general treatment is the same as for oriental sore; ten to twenty intravenous injections of antimony tartrate (20–30 gr.) or of the pentavalent compound, neostibosan, suffice for cure. The local ulcers on the lips and nose are cleaned up with fomentations, the cleansed surfaces anesthetized with a mixture of cocaine, menthol, and carbolic acid, then sprinkled with finely powdered antimony tartrate and bound up with a bandage. Subsequently the wounds are dressed with an ointment composed of zinc oxide, bismuth, and lanolin. From the buccal mucosa scabs

must be removed with a solution of bicarbonate of soda, the surface anæsthetized with cocaine (1 per cent.) and sprayed with 1-2 per cent. antimony tartrate solution. Berberine swabs, on pledgets of cotton wool, are applied to the nasal mucosa.

Mazza and others in northern Argentina had good results with intramuscular injections of *Fouadin* (or stibophen), a trivalent antimony compound, in doses varying from 0.5 to 5 ml. The treatment was continued for varying periods. Twenty to thirty injections are usually necessary and, according to Schulemann, the results continue to be satisfactory.

Good results were obtained by intramuscular injections of *Eparseno* (dioxy-diamido-arsenobenzol), prepared by Poulenc Frères, Paris. Injections of 0.12 to 0.25 grm. (1-2 ml.) are given and as many as 10-20 injections at intervals of two to three days are necessary. Others obtained success with similar injections of the double iodide of quinine and bismuth (0.15 grm. daily for one month). Atebrin (mepacrine hydrochloride) injections are advocated by Mazza and Cornejo in isolated sores: 5 ml. of a 10 per cent. solution are injected into the base of the sore and three tablets given by the mouth for seven days. Penicillin has also been used with success. Streptomycin injections, thiozamide, anthiomaline, *N. methyl glucamine antimoniate* (glucantime) have also been used (Casile and Saccharin).

In assessing the relative value of the various treatments, it must be remembered that spontaneous cure appears to take place in about 7 per cent. of cases (Pessoa).

Prophylaxis.—Spraying with DDT and other measures against sandflies (p. 859) have been generally successful. In the municipality of Mage (Rio de Janeiro), where espundia is prevalent in forested areas with high rainfall, and scattered rural population, 12.7 per cent. had ulcers of the leishmanial type, the disease has been suppressed since 1953 after 5 years application of DDT (Guimaraës and de Bustamente).

Subsection B.—FEVERS CAUSED BY BLOOD * SPIROCHÆTES AND SPIRILLA

CHAPTER VII

RELAPSING FEVERS

Synonyms. Febris Recurrens; Spirillum Fever; Famine Fever; Tif Fever; Bilious Typhoid of Griesinger.

Definition.—A group of diseases, characterized by fever of sudden onset and, after several days (one to seven), rapid subsidence, which may relapse at intervals of from one to seven or more days for an indefinite number of times. They are caused by spirochætes, which are present in the blood during the fever and are transmitted by the body-louse (*Pediculus*) or by certain ticks (*Ornithodoros*).

Geographical distribution.—*Louse-borne relapsing fever.*—*Europe.*—Formerly in Britain, especially Ireland, also Norway, Denmark, Russia, Turkey, Bulgaria, Rumania, Yugoslavia. *Africa.*—Egypt, N. Africa, N. Equatorial Africa (South of Sahara), Ghana, Sudan, Kenya Highlands, China, Manchuria, and South Persia (Abadan), India—Central Province and N.W. Frontier. (A virulent epidemic, associated with jaundice, commenced in 1921 in N. Equatorial Africa, spreading across the Continent at 15° N. and continued for over seven years. Thence it extended to Senegal and the Gold Coast to upper Guinea, French and British Nigeria, Wadai and West Egyptian Sudan. In clinical manifestations and virulence it resembled Yellow Fever.) *African Tick Fever.*—Senegal, Congo, East Africa, Uganda, Abyssinia and Madagascar, Transvaal (Kimberley), Cape Province (Græff-Reinet), Somaliland. *W. American Tick-borne Relapsing Fever.*—Colorado Valley, Texas and California. *Central and S. American Relapsing Fever.*—Panama, Venezuela and other S. American States. *Other Tick-borne forms.*—Spain, Morocco, Cyrenaica, Palestine, Cyprus, Turkmenistan, Syria and Persia.

Ætiology.—The various clinical forms of relapsing fever are caused by *Spirochaeta recurrentis*, or organisms which are morphologically indistinguishable from it, but which may be biologically separable, such as *S. duttoni* and *S. venezuelensis*. (In American literature the generic term *Borrelia* is used for these spirochætes and is gradually gaining acceptance).

Typically, the spirochæte is a delicate spiral filament; its length varies from 8 to 15 μ , and its width from 0.2 μ to 0.3 μ . Each turn has an amplitude of 2 to 3 μ . The body of the parasite may have three, four, or six bends or turns; dividing forms appear to have more; in fact, the body of the spirochæte undulates, it does not strictly form a spiral. Coles described the minute structure as

consisting of small granules in a containing tube and by the electron microscope flagella can be demonstrated. Swain has described the appearances under great magnification as follows: The outer covering is of structureless material. The sharp, clear-cut outline and constant diameter of the underlying body suggest that it is contained by a cell membrane. Wound round the body, and apparently embedded in the outer coat, are 7-11 fine fibrils which are attached to the body subterminally. It is suggested that the appearances differ in *Sp. duttoni* from those of *Sp. recurrentis*. In the latter organism the appearances are of a 2-strand flex which, in turn, is composed of a bundle of 12 fibrils twisted spirally round the body. By the Romanowsky method the body of the parasite usually stains uniformly, with the exception of the extremities, which are pointed and take only a very faint tint. In fresh blood the spirochaetes exhibit very active screw-like movement; some are longer than others, the long forms resulting from end-to-end attachment of two or more parasites. That this is the explanation of the long forms, which may measure from 16 to 100 μ , is shown by staining. In those measuring from 16 to 18 μ we find a pointed extremity at each end of the filament and a pale zone in the middle, the pale zone corresponding to the approximated lightly staining extremities. The still longer forms admit of a similar explanation. Although the normal habitat of the spirochaetes is the liquor sanguinis, occasionally in fresh liquid blood preparations, they are seen within the red blood-corpuscles, though this probably does not occur within the body.

Great variation is shown in morphology, but there is a consensus of opinion now that no constant distinctions exist between the organisms in the different clinical forms of the disease. For an explanation of the nomenclature the reader is referred to Table II.

Demonstration of the spirochaete.—The parasite occurs in the blood during the febrile stage of the disease only when the temperature is above 102° F., often disappearing some forty-eight hours before the crisis and being very scarce or entirely absent during the non-febrile intervals. In some forms and cases it is present in large numbers in every field of the microscope; in others it is so scanty that many fields have to be examined before a single specimen can be discovered. In thin films of fresh blood it can usually be recognized by the agitation its movements communicate to the adjacent corpuscles (Fig. 37). In dried and fixed films the stains in general use for malaria work suffice.

In children, especially, the spirochaetes may often be found sparsely in the blood-stream during the apyretic periods.

Dark-ground illumination is admirably adapted for demonstrating the living parasites. Occasionally, when very scarce in the blood-stream, as during a relapse, or in the clinical form met in North Africa, the organism may best be demonstrated by the "thick-film" method. Chung in China has demonstrated these spirochaetes in the urine, but this appears to be quite exceptional.

Cultivation.—The successful cultivation of *S. recurrentis* and its sub-varieties was first obtained by Noguichi and others in sterile ascitic fluid containing citrated blood and a small amount of fresh kidney, incubated at 37° C. The greatest multiplication of the organisms takes place at the junction of the ascitic fluid and of the blood. Anaërobiosis is necessary and also the presence of coagulated albumin. The pH value of 7.2 is of great importance. The spirochaetes reach

their maximum development on the seventh to the ninth day, after which they begin to disintegrate. Subcultures retain their virulence for mice.

Chen in Peking obtained cultures on chick embryo. Blood containing *S. recurrentis* was inoculated beneath the chorio-allantoic membrane. A good growth of spirochaetes was seen in the blood of the embryo reaching its maximum on the fifth day.

Meleney found that the grey squirrel (*Sciurotamias davidianus*) and the striped chipmunk (*Tamias asiaticus*) can be experimentally infected with the Chinese strain. After splenectomy the virulence of the attacks in these animals was increased.

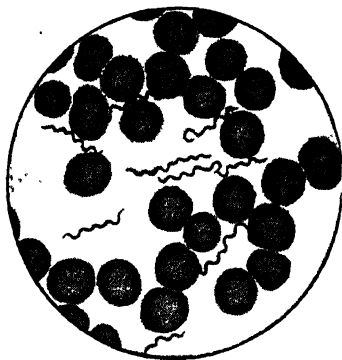


Fig. 37.—*Spirochæta recurrentis* in blood-film. $\times 500$. (Microphotograph: Dr. John Bell.)

Different strains of relapsing-fever parasites (see Table II, p. 173).—

The parasite, as originally described in Europe, is known as *S. recurrentis*. The Persian form of the disease (mianeh fever) is considered to be clinically distinct, and due to *S. persica*. The Central African disease, popularly known as tick fever (or carapata disease), is due to *S. duttoni* transmitted by *Ornithodoros moubata*. The South American form is known as *S. venezuelense*. In Colombia and Ecuador it is transmitted by *O. venezuelense* (or *O. crossi*). In 1926 de Buen described a new variety, more resembling the Central African form,

transmitted by ticks (*Ornithodoros maroccanus* and *O. erraticus*) which live in the burrows of rats and porcupines, and the parasite has been named *S. hispanica*. In Turkmenistan a strain (*S. persica* or *S. sogdianum*) has been found to be transmitted by *O. tholozani* and in other parts of the U.S.S.R. by *O. tartakowskii*, the former of which has proved to be the carrier there and also in Cyrenaica (Tobruk), Palestine, Cyprus, Persia and N.W. India. *S. latychevi* was found by Baltazard and others (1952) in Meshed province of Persia and is transmitted there by a small species—*O. tartakowskii*. The animal reservoir is probably the merion (*Meriones lybicus*). The infection is slight. In Kashmir and Jammu the spirochaete is transmitted by *O. crossi* (*O. rudis*).

Clark and Graham originally suggested that a tick-borne infection might occur in the Colorado Valley, Texas, and in California. Now it has been described by Wheeler, Herms and Meyer as due to *S. turicata*. It is transmitted by *Ornithodoros hermsi*, *O. turicata*, and possibly by *O. parkeri* (see Appendix, p. 1029).

White mice and white rats are especially susceptible to these spirochaetes, the former particularly so, the organisms appearing in the blood within twenty-four hours of inoculation and persisting to the third day. About this time they disappear for several days from the blood until the commencement of the first relapse, which may be followed by a second, third, or even a fourth, the number varying in individual mice; with each relapse the parasites reappear in the blood. The interval between the relapses is

TABLE II
SYNOPTICAL TABLE OF VARIOUS FORMS OF *SPIROCHÆTA* AND CLINICAL SYMPTOMS
OF THE RELAPSING FEVERS THEY EVOKE IN MAN

Habitat and Strain.	COSMOPOLITAN: N. AND S. AMERICA. N. AND W. AFRICA. N. CHINA. EUROPE. INDIA	TURKEMENISTAN, PARSIA AND UNDO- WEST INDIA.	SOUTH SPAIN AND MOROCCO.	CENTRAL AFRICA.	CALIFORNIA, TEXAS, IDAHO AND COLORADO.	CENTRAL (PANAMA) AND S. AMERICA (COLOMBIA AND VENEZUELA).
<i>Spirochæta recurrentis</i> (<i>obermeyer</i> , <i>nory</i>).	<i>Spirochæta persica</i> (<i>goy- dattum</i>).	<i>Spirochæta persica</i> (<i>goy- dattum</i>).	<i>Spirochæta hispanica</i> .	<i>Spirochæta duttoni</i> .	<i>Spirochæta turicata</i> .	<i>Spirochæta senecadenata</i> (<i>neotropica</i>).
Animals susceptible.	Small rodents, only after passage through mon- keys.	Monkeys (<i>Macaca</i> , <i>Cercopithecus</i>) rats, mice, field mice, guinea- pigs, hamsters, dogs, rabbits, badgers.	Guinea-pigs, desert foxes, jackals, Moroccan hedgehogs, rats, mice and shrews.	Small rodents and many animals susceptible.	Chimpanzees (<i>Tamias</i> Sp), armadillos, squirrels (<i>Sciurus douglasii</i>)	Rs. American monkeys, marmosets (<i>Leopoldo jacchus</i>), opossums (<i>Didelphis marsupialis</i>), armadillos (<i>Dasypus novemcinctus</i>).
Course in animals.	Mild.	Severe.	Severe.	Very severe.	Fairly severe.	Severe.
Subinoculations in animals.	Monkey to monkey, mouse to mouse. Per- sisting brain lesions.	Monkey to dog, rabbit and guinea-pig.	Guinea-pig to guinea- pig.	Monkey to monkey positive. Shrew-mice (<i>Crocidura</i>) and rats in Dakar. Brain infections.	White mouse to mouse and squirrel.	Marmoset to marmoset.
Course in man.	2-4 relapses. Incubation period 2-10 days. Dura- tion of attack 5-6. Apyrexia 7-10.	Fairly severe attack, usually short, average 2-8 days. Relapses 1-14. Ocular complica- tions severe.	Apparently resembles the Central African form. Fairly severe with 4-6 relapses of 3-4 days each.	Severe: 5-11 relapses. Incubation period 7- 10 days. Duration of first attack 3. Apy- rexia. 1-8. Complica- tions severe.	Resembles cosmopolitan form.	Resembles Central African form. Many cases benign.
Natural transmitters.	Lice (<i>Pediculus humanus</i>).	Ticks (<i>Ornithodoros tho- losani</i> (<i>papillipes</i>), <i>O. laborensis</i> and <i>O. crossi</i>	Ticks (<i>Ornithodoros erraticus</i> or <i>O. maro- canus</i>).	Ticks (<i>Ornithodoros monaudi</i> , <i>O. erraticus</i>). Hereditary transmission.	Ticks (<i>Ornithodoros hermsi</i> , <i>O. turicata</i> Texas, ? <i>O. parkeri</i>).	Ticks (<i>Ornithodoros sen- sudente</i> , <i>O. turicata</i> , <i>O. leishae</i>).
Serum reactions.	Immune serum not agglu- tinating <i>S. duttoni</i> .	Large numbers of strains without cross- immunity.	Immune serum not agglutinating <i>S. re- currentis</i> .	Immune serum not agglutinating <i>S. re- currentis</i> .		Immune serum not agglutinating <i>S. duttoni</i> .

N.B.—In all tick-borne infections transmission is hereditary: this does not occur in the louse-borne disease
A new species is described as *S. laydecti* from Meshed, Persia, transmitted by *Ornithodoros tartakovskyi*.

generally about seven days ; occasionally it is only two, though it may be as many as ten. The actual number of organisms in the blood in the first is greater than in subsequent relapses, indicating the development of a partial immunity. Recovery in mice is the rule.

As a result of the consecutive passage of the spirochæte through a long series of rats its virulence is augmented, so that the incubation period becomes reduced to 15-18 hours, and the persistence of the parasite in the blood is prolonged to 60 hours instead of, as originally, 48 hours ; at the same time they become far more abundant.

Some spirochætes have a definite neurotropic tendency and, after subinoculation of *S. duttoni* in mice, a residual brain infection persists. According to Adler this also takes place in small wild rodents and squirrels which form the reservoir of infection.

In rats an acquired immunity may be produced which lasts for many months. As a rule, *S. duttoni* produces a far more severe disease in these animals than does *S. recurrentis*.

Rabbits and guinea-pigs are relatively refractory.

Dogs, rats and guinea-pigs are refractory to *S. venezuelensis*. Man and certain squirrel monkeys seem to be the chief reservoir of this spirochæte. Mice which have been made immune to *S. duttoni* can subsequently be infected by *S. venezuelensis*.

Pathology.—The spleen is usually large and soft, often shows multiple infarcts, necrotic nodules and may rupture spontaneously. Sudden intrasplenic hæmorrhage has been recorded. Perisplenitis is common. Sterile abscesses may also form. In the 1945-46 epidemic in Egypt, El-Ramly found in 3,000 cases that 2·5 per cent. had infarctions of which 0·77 per cent. developed splenic abscess. Secondary infections of the abscess cavity may ensue. Sections of the spleen and liver show spirochætes within the endothelial cells and they are very abundant in necrotic lesions in the Malpighian bodies and constitute an important basis for differential diagnosis from yellow fever. Liver, kidneys, and heart show cloudy swelling of their cellular elements. The skin in fatal cases is usually jaundiced and there may be subcutaneous petechiæ. The bone-marrow is hyperæmic, shows great activity of the leucoblastic elements and there is generally a marked polymorphonuclear leucocytosis. Spirochætes are often phagocytosed by the leucocytes, but disappear rapidly after death. During the apyrexial periods an occasional spirochæte may be seen in the peripheral blood. Before a negative result can be claimed not less than 0·25 ml. must be injected into a susceptible animal which must be examined twice daily for at least ten days.

Sagel showed that infection produced by the bite of a tick is much more virulent than that brought about by direct inoculation. Relapsing-fever spirochætes are remarkably neurotropic, and in guinea-pigs the brain and cerebellum are still infective fourteen months after primary inoculation. A great deal of attention has recently been paid to this fixation in the brain of mice and birds. Similarly, Mathis and Durieux showed that strains of *S. duttoni*, originally isolated from shrew mice in Dakar, may persist in the brains of subinoculated mice up to 235 days.

Transmission.—There are two main forms of intermediary host which transmit relapsing fever, namely lice and ticks. A reservoir of infection of relapsing-fever spirochætes has been thought to exist, especially in Africa, in small rodents. Thus Nicolle and Anderson in Tunis suggested that the spirochæte of these mammals, *S. normandi*, may be identical with *S. duttoni* (but Heisch has recently disproved this). This latter organism is virulent to rats and mice, but not pathogenic to guinea pigs. The *hispanica* strain is equally virulent to mice, rats and guinea pigs.

Russel in Accra (Ghana) and Boiron in Dakar found the pouched rat (*Cricetomys gambianus*) to be most susceptible to infection with *S. duttoni*, and suggested that the spirochæte of the shrew mouse, *S. crociduræ* and that of the rat (*R. alexandrinus*), may be identical with *S. duttoni*. In Panama, Clark and Dunn found a Geoffroy's squirrel monkey—*Saimiri ustula*—naturally infected with *S. venezuelensis*.

Congenital transmission.—There are several records of new-born infants developing relapsing fever within 10 days of birth and no less than three were in triplets. It is difficult to explain, in view of the usual interval of one week or more, between the actual birth and first evidence of the disease (Bell, 1952).

Epidemiology and endemiology.—The fever caused by *S. recurrentis* occurs, as a rule, at definite seasons of the year, depending upon the circumstances which favour the propagation of the intermediary host, the body-lice. In times of peace the poorer and indigenous class of the community is attacked. In Europe, for instance, relapsing fever has been a feature of famine, as has long been noted in Ireland, where it was once known as "famine fever." Widespread epidemics have occurred among the partially starved population of Central Russia. In war-time it is the scourge of armies in the field, and is commonly associated with epidemics of typhus, also a louse-borne disease; therefore the two infections may co-exist, as in the great Serbian epidemic of 1915. In Southern Europe and Northern Africa relapsing fever is a disease of the winter and spring months, at which time people are wont to envelop themselves in thicker clothes and to congregate together for warmth, thus facilitating transmission. Alarm was caused by the rapidly advancing and widespread epidemics of louse-borne relapsing fever which swept across Africa in 1921, starting from Upper Guinea. In two years the number of deaths caused in the French Sudan and the Niger was estimated at 80,000–100,000. In the upper Volta area it caused 20,000 deaths, and in 1926 in Darfur over 10,000. Generally speaking the louse-borne disease is uncommon in Equatorial Africa, on account of the scantier clothing worn. In Dakar and certain parts of Senegal, however, the infection is tick-borne, and the spirochæte is said to be identical with *S. duttoni*. In India it has been noted that at the advent of the hot weather, in April and May, the lice die off and the epidemics of relapsing fever come abruptly to an end.

The epidemiology of tick-borne relapsing fever differs from that of the louse-borne disease, as the former is associated with houses and localities which form a suitable environment for *Ornithodoros*, and is transmitted in

a hereditary manner. In Central Africa it has been known for many years that the "rest-houses" on the main routes of travel are endemic centres of this fever, for the ticks live in the mud walls and roofs of the huts, and emerge at night-time to feed on man. There is therefore no seasonal incidence as in louse-borne relapsing fever. The same has been noted in the South American tick-borne form, except that a greater incidence is observed in the wet and rainy season, when native labourers and oil prospectors are necessarily more confined to their quarters.

In Israel and the Middle East caves in wadis are a frequent source of infection, and those who explore them are liable to be bitten by *Ornitho tholozani*. This has recently been recorded in the Jordan Valley in the quest for the Dead Sea scrolls.

Evolution of the parasite in the intermediary host.—Philip Ross, Milne, Dutton and Todd showed definitely that *S. duttoni* is normally conveyed by *O. moubata*, and that it can be transmitted, not

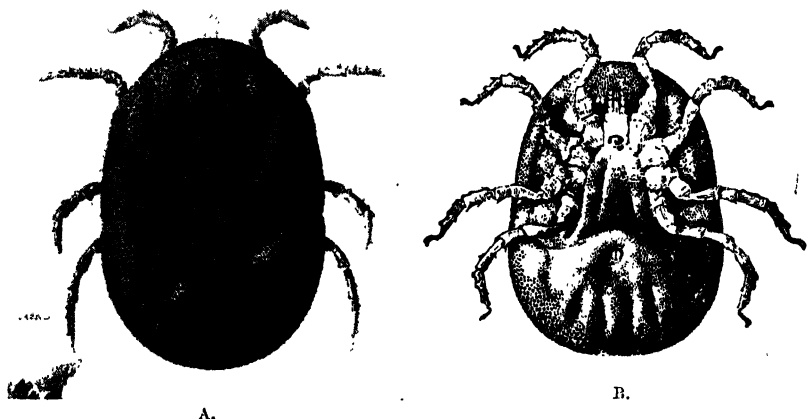


Fig. 38.—*Ornithodoros moubata*, Murray, ♀. $\times 4$. (After Smart).
(By permission of the British Museum (Natural History).)
A. dorsal; B. ventral view.

only by the tick which has bitten the infected individual, but also by its progeny, even to the third generation (Koch). The spirochæte has been demonstrated within the eggs laid by infected ticks. From these eggs nymphs are produced in which the organism multiplies. Once fed on spirochæte-containing blood, ticks remain infective for one and a half years, and can convey relapsing fever by successive bites to at least ten monkeys (Fig. 38).

Wheeler, Herms and Meyer found a tick vector in California in *Ornithodoros hermsi*, which they collected from Lake Tahoe, Big Bear Lake, San Bernardino, Eldorado and Placer counties, at an elevation of 5,000–8,000 feet. These ticks were found naturally infected with the Californian strain, and produced infection in mice and monkeys. Chipmunks and squirrels, which abound there, seem to be the reservoirs of infection. Ticks

fed on the Sierra Chickaree squirrel (*Sciurus douglasii*) infected a monkey. The most northerly focus is Mount Lassen at 5,800 feet. The bites of both male and female ticks in all instars are infective.

Development in the tick.—The cycle of development differs from that in the louse in that some spirochætes enter the solid organs of the tick, the cells of the gut, the Malpighian tubules, and the coxal and salivary glands. Some can even be found in the ovaries (transovarian transmission, which can continue indefinitely). They remain motile for several days after ingestion into the stomach, the duration depending on temperature. Complete development usually takes about ten days.

Transmission is effected by the saliva and secretion from the coxal glands. When the tick feeds on blood it makes a relatively large puncture in the skin and the saliva is delivered at the base of the mouth parts, so that presumably none enters the wound, but towards the end of feeding the tick evacuates the contents of its hind-gut, consisting partly of fæces and partly of nitrogenous waste from the Malpighian tubes. Lavoipierre and Riek have investigated the feeding habits of ticks minutely. The actual feeding time varies with the species—*O. erraticus* feeds more rapidly than *O. tartakowskii* or *O. moubata*. The penetration of the host skin by the mouth parts was observed by trans-illuminating the ear of a mouse on which the ticks were feeding. Blood from the tissues lacerated by the cheliceral digits was sucked up. This sucking activity alternated with periods during which saliva was pumped in. As the ticks near repletion, blood spreads into the surrounding tissues from the point of entry of the mouth parts; this spread was aided by an anticoagulin and diffused by a spreading factor resembling hyaluronidase present in the saliva. Fluid containing spirochætes is also excreted from the coxal glands through an aperture at the base of the front legs. In *O. moubata* this occurs while the tick is still feeding. (Fig. 38B.)

Transmission has been proved to be direct by bite from *O. tholozani* (Adler) and *O. hermsi*, as these ticks do not pass fæces or coxal fluid when biting. If the puncture wound in an experimental animal be scraped and smears made spirochætes can readily be demonstrated. Relapsing fever spirochætes may survive within ticks for as long as 6½ years.

Development in the louse.—The louse absorbs 1 mgm. of blood, which may contain large numbers of spirochætes (*S. recurrentis*). One day after ingestion they may be discovered in the insect's midgut (at 28° C.: 82° F.). At this stage some attach themselves to the epithelial cells lining the midgut; others invade the cells, while many die in the gut. By the end of the first day the spirochætes have disappeared, and there then follows a phase during which they can seldom be found in any part of the body. This was thought to be a "granular" phase, as in the tick, but the correctness of this question is difficult to decide as the tissues contain so many other kinds of granules. Adler and others now reject this theory and consider that the organisms persist as spirochætes, though difficult to find. After the eighth day (or even after a few hours—Chung and Feng, 1936) spirochætes appear in the blood of the louse, circulating through its body cavity. They then increase rapidly and may be found in all parts of the body and limbs, but not in the lumen of the gut or within the salivary

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glands and ducts. These fully developed, or metacyclic spirochaetes, persist in the body of the louse throughout its life, without causing any ill effects. Thus, a considerable proportion of lice taken from a relapsing fever patient may be found infested (Fig. 89).

When the spirochaetes have reached the body cavity they have no natural means of egress and the louse can then bite man with impunity, but if a leg or antenna is injured or broken, the spirochaetes escape and will enter any scratch or abrasion. Transmission probably normally takes place by man rupturing the louse with his nails and inoculating himself while scratching. As crushing kills the insect, one louse is capable of

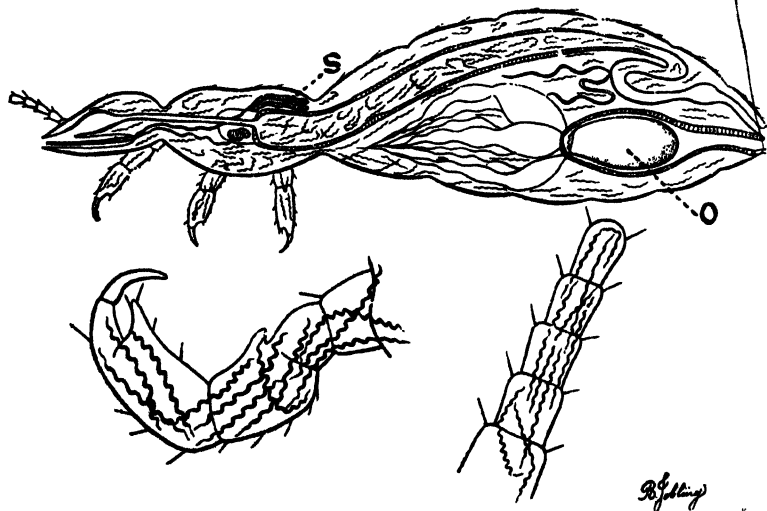


Fig. 89.—*Spirocheta recurrentis* of relapsing fever and its development in the louse (*Pediculus humanus*). (C. M. Wenyon, Trans. Roy. Inst. of Great Brit.)

Diagram shows whole body invaded by spirochaetes. S, salivary glands; O, egg. Below, spirochaetes in leg and antennae, which are easily broken off, so that fluid exuding from the body infects the skin of the host.

producing relapsing fever merely in one individual and, therefore, for this disease to assume epidemic proportions, lice must be extremely abundant.

Under optimum conditions 48 per cent. of lice become infected and remain so for 28 days. It is very unlikely that any spirochaetes escape in louse excreta. There is no evidence of hereditary transmission in this insect. According to Adler *S. persica* strains may sometimes be isolated from lice. (The crab louse, *Phthirus pubis*, appears incapable of transmitting the spirochaete.)

Heisch in 1949 and later Mooser and Weyer (1954) have succeeded in reversing the customary role of *Ornithodoros* by infecting lice with *S. duttoni*, by feeding them on mice, or by rectal or intracoelemic inoculation with the blood of infected mice. After intracoelemic inoculation spirochaetal growth was so vigorous that within a few days it was teeming with them. When put back into mice after the 21st louse transfer the strain

behaved like the original with respect to its immunologic properties as well as its infectivity for *Ornithodoros moubata*.

Patients can be inoculated by scarification of the skin with coelomic fluid of lice infected with *S. recurrentis* (Sparrow, 1954).

Other methods of transmission.—The spirochætes have been proved capable of penetrating the mucous membrane and, if well rubbed in, the unbroken skin. Nurses and doctors treating relapsing-fever patients have been inoculated through the entry of infected blood into the conjunctival sac, and in pregnant women and experimental animals it has been proved that the organism can pass through the placenta to the foetus. A particularly virulent infection is commonly found in China in heroin addicts, conveyed by dirty syringes, just like subtertian malaria (*see p. 37*).

Immunity.—Sabritschewsky, in 1896, showed that, when equal parts of spirochæte-infected blood or serum and normal serum are mixed, the spirochætes survive longer than when the infected blood is mixed with that of a patient who has recovered from relapsing fever. He accordingly concluded that the cause of the crisis in relapsing fever and of subsequent immunity was the development of some germicidal substance in the blood. He was the first to apply serum-therapy, and to obtain an anti-spirochætal serum by repeated inoculation of the horse with human spirochæta-containing blood.

Treated *in vitro* with hyper-immune serum, the spirochætes rapidly become unrecognizable aggregations of granules; this phenomenon may be manifest in a dilution of 1 : 2000.

Cunningham in 1925 showed that the spirochætes (*S. recurrentis*) which are found in the blood in the initial attack differ serologically from those which bring about the first relapse, and, on inoculation into animals, these strains maintain the same characteristics. Thus, if strain A be inoculated into an experimental squirrel, the initial attack will be of that serological strain, but in the subsequent relapse the strain will be B; but if the B strain be inoculated, the relapse will be A, and so on. There is thus an alternation of serological strains. It is probable that the antibodies produced in the blood-stream by one particular strain do not persist long enough to prevent relapses. The thrombocytobarin (Rieckenberg), or adhesion phenomenon, shows clearly that serological differences exist between spirochætes of the first attack and those of the second. On the other hand there are numerous immunological strains of tick-borne spirochætes, even in the same endemic area.

GENERAL SYMPTOMS COMMON TO ALL FORMS

I. EPIDEMIC COSMOPOLITAN LOUSE-BORNE TYPE (*Spirochaeta recurrentis*).—The course and character of the disease vary greatly in a single epidemic, and, further, the virulence of the more severe forms is much greater in some outbreaks than in others. The *incubation period* usually lasts from two to ten days. In some instances the attack develops promptly on exposure; but is never delayed beyond the fourteenth day. In those artificially inoculated symptoms show themselves in from two to six days.

The *onset* is generally abrupt, being characterized by chilliness or rigor, giddiness, epistaxis, vomiting, photophobia, intense headache, and pain in calves. In the young there may be convulsions. Temperature rises rapidly to 104° or 105° F (40–40.5° C.) rarely to 108 (42.5°C.) (Chart 8). The pulse is rapid, 110 to 180. Should fever run high, there may be delirium. The skin is dry, although, especially during the first day,

occasional sweats may break out. A slight icteric tinting of the conjunctiva is usual and, not infrequently, jaundice is marked at the crisis. The spleen is invariably enlarged and tender. The tongue is coated and moist, except in severe cases, when it may become dry, brown, and painful on protrusion. The bowels, as a rule, are confined; abdominal pain may be considerable, and patients usually complain of pains in the muscles of the legs, especially the calves. Occasionally, herpes labialis is noted. There is quite commonly an erythematous rash in the initial fever, and later, rose-coloured spots on the trunk and limbs. Some authors describe petechiæ. The rash has a peculiar distribution, being generally most marked round the neck, spreading in a semicircular fashion from the mastoid processes; thence it ranges symmetrically round the shoulders, down the sides of the chest and abdomen to the inner aspect of the thighs, and to the extensor and flexor aspects of the forearms. The individual petechiæ may be as large as a threepenny bit, and need to be carefully differentiated from the exanthemata of typhus and hæmorrhagic smallpox. They are not easily detected on a dark skin.

Taft and Pike also describe a skin eruption resembling erythema multiforme which persists for one or two days. In biopsy made from the superficial layers spirochætes were demonstrated, even during the afebrile period. This is the first recorded instance of the discovery of these spirochætes in the skin.

The primary remittent fever may last from five to seven days. At first the morning is usually lower than the evening temperature, but on or about the third day the evening temperature rarely rises above that of the morning. On the fourth, fifth, or sixth days there is again a rise of temperature, sometimes with delirium, ending in a crisis of profuse sweating and diarrhœa. The temperature now falls rapidly to normal or subnormal, sometimes dropping in a few hours as much as 12° F.; in elderly or delicate patients there may be dangerous collapse.

The initial pyrexia, or *first paroxysm*, is followed by a *first period of apyrexia* during which the patient recovers so rapidly that after four or five days it may be difficult to keep him in hospital. But from seven to nine days after the crisis, that is about the fourteenth from the commencement of the attack, rigor again occurs, followed by a second attack of fever—*first relapse*. This may be more severe than the initial paroxysm; usually it is milder, and seldom lasts so long. During it the secretion of urine is considerably increased; sweating also is profuse, and prostration marked. A polymorphonuclear leucocytosis of 15,000 to 30,000 is found during the pyrexial periods.

With the defervescence of the first relapse the patient enters on the *second period of apyrexia*, which usually coincides with convalescence (Chart 8). But in some patients a *second relapse* may occur, usually about the twenty-first day, counting from the onset of symptoms. This second relapse rarely lasts longer than three days, and is generally milder than the previous paroxysms. In rare instances three, four, five or even more relapses have been observed. Anomalous types of fever are common. Some temperature charts show an intermittent fever throughout, somewhat resembling that of phthisis. Cases with four relapses in a period of

twenty-six days are met. Occasionally the apyrexial period may be of considerable length—seventeen days; in one case in particular, forty-two days. In some epidemics chronic diarrhoea, in others arthritis, are a feature.

Convalescence may be protracted, and complicated with such sequelæ as nephritis, ophthalmia, iritis, œdema of the eyelids, otorrhœa, polyarthritis, pneumonia, neuritis, parotitis, and adenitis. A mild type of encephalitis has been recorded (1943). In pregnant women abortion is the rule. In some cases attacks of abdominal pain resemble appendicitis. Spontaneous rupture of the spleen has been recorded. In one instance this organ weighed 315 grm.

BILIOUS TYPHOID FORM.—This is thought by some to be a distinct disease and, on account of the severity of its symptoms and rapidity of its course, especially on the West Coast of Africa, is apt to be mistaken for yellow fever. High fever, epistaxis, dyspnœa, intense jaundice, and

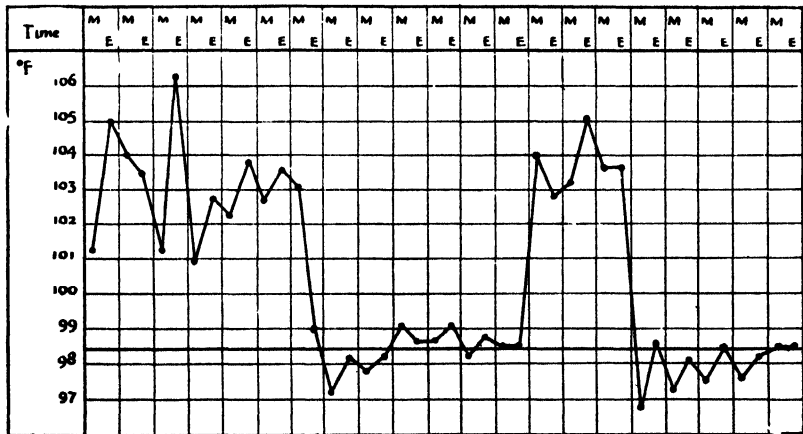


Chart 8.—Relapsing fever, cosmopolitan louse-borne type.

enlargement of the spleen are noted. The jaundice is probably due to toxic hepatitis. The liver is enlarged. The purpuric rash is a thrombocytopenic purpura and is associated with hæmorrhages from the mucous membranes. Hæmorrhages into the skin and from the internal organs commonly occur; marked albuminuria is the rule.

Some cases become stuporose, with tympanites, hiccup, and severe diarrhoea. In Abyssinia intense dyspnœa was a prominent feature. These severe forms are more generally seen in war-time, when in association with starvation and exhaustion, the disease assumes a more serious aspect.

II. PERSIAN TYPE (mianeh disease).—This tickborne type is due to *Spirochaeta persica* (*sogdianum*). It is found throughout Persia, and apparently also in Syria, Cyprus, Libya and Palestine. The symptoms may be said to be intermediate between those of the epidemic louse-borne and those of the Central African type, for, as compared with the former, the relapses are more numerous and of shorter duration, while the spirochaetes

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are very scanty in the peripheral blood, requiring a thick-drop method for their demonstration (Chart 9). According to Adler, who has worked in Palestine, these attacks may, on occasions, be severe and eye complications frequent. Splenic infarcts and intra-splenic hæmorrhages are common. Jaundice may supervene and the mortality may be high. The attack is generally moderately severe; the initial pyrexia shows marked morning intermissions, and lasts four to five days, when the temperature falls either by lysis or by crisis. Three, four, five or even more relapses are often noted, lasting sometimes only twenty-four hours, or, at a maximum, three days.

III. CENTRAL AFRICAN TYPE (carapata disease; tick fever; *gord* Somaliland) (*Spirocheta duttoni*).—The African tick-conveyed relapsing fever, caused by *S. duttoni*, although in type of fever resembling the epidemic European and Indian forms, differs in some important particulars. The initial fever is not usually so prolonged, generally terminating by

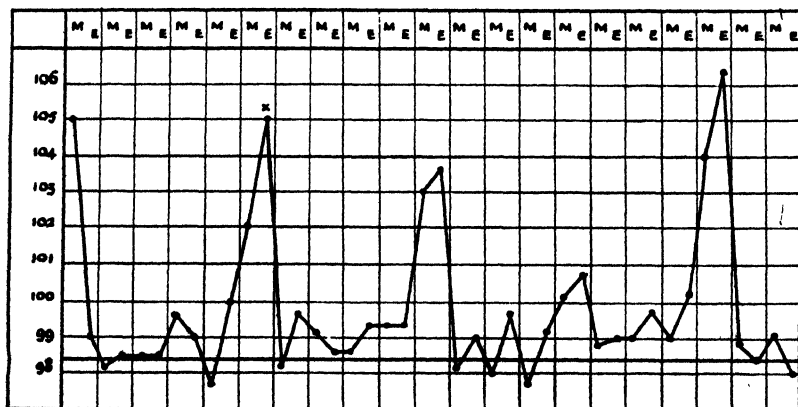


Chart 9.—Relapsing fever, Persian type. (Bellingham Smith.)

X Spirochetes demonstrated in blood-film.

crisis within three days. Diarrhoea and dysenteric symptoms are not uncommon. The apyrexial intervals are of very irregular duration, being, according to Philip Ross, sometimes as short as one day; sometimes as long as three weeks; and instead of only one or two relapses, as in ordinary relapsing fever, there may be as many as eleven; five or six relapses being the rule (Chart 10). The fever, though shorter, is as severe in the relapses as in the initial paroxysm, but the intervals tend to become longer, though there are exceptions. Sometimes the fever may assume a low chronic form, associated with a sharp cutting pain in the nape of the neck and vomiting. Iritis or iridocyclitis, uni- or bilateral, is a not uncommon complication or sequela. The liver and spleen are generally enlarged, and jaundice, bronchitis and pneumonia are frequent complications. The parasites, usually very scanty in peripheral blood, may be hard to find. There is a polymorphonuclear leucocytosis, as in the louse-borne type, and a slight microcytic anæmia.

Fulminating cases, in which the onset is very sudden, were observed nine times in a study of 1,500 cases during the East African campaign (1914-1918) by J. K. Manson and Thornton. In these the spirochaetes occur in enormous numbers; coma and death may ensue within twenty-four hours. Sometimes there is most intense icterus. These observers considered that death is brought about by impaction of masses of tangled spirochaetes in the cerebral capillaries.

In natives of the endemic districts the disease, as generally observed, is not nearly so severe as in Europeans and strangers, being usually limited to a paroxysm or two of one or two days' duration. The mildness of these attacks is probably explained by a partial immunity conferred by previous infections. Charters has stated that the tick-borne relapsing fever in Somaliland is less severe than the louse-borne in Abyssinia.

Implication of the central nervous system, due to invasion by spirochætes, is not uncommon. A particularly distressing, but fortunately



Chart 10.—Relapsing fever, Central African type. (*Newham.*)

somewhat rare, complication is optic atrophy. Of this there are two forms—one which follows immediately upon the cessation of the fever, the other which gradually develops after the lapse of several months. Some observers have described aphasia, facial paralysis, hemiplegia, and implication of the cranial nerves—such as the third, fourth, and sixth (resulting in ptosis and strabismus), the fifth (trigeminal neuralgia), the seventh (facial paralysis), and the eighth (deafness)—coming on suddenly during the course of the disease; others have recorded signs of meningitis. In these nervous complications spirochaetes may sometimes be demonstrated in the cerebro-spinal fluid; as a rule, it contains an excess of lymphocytes and is under considerable pressure, necessitating lumbar puncture in order to relieve symptoms. Hawking in Tanganyika failed to find spirochaetes on microscopic examination of cerebro-spinal fluid, though an intraperitoneal injection into mice produced infection. In patients infected with subtertian malaria a superimposed attack of relapsing fever may determine the onset of blackwater fever. Arthritis is not uncommon.

IV. TICK-BORNE SPANISH TYPE (*Spirochaeta hispanica*).—The most complete study of the clinical aspects of this form of relapsing fever is by Más de Ayala (1931). The incubation period is apparently very short, 1–2 days, and the onset of the fever abrupt. It is ushered in by nausea, headache, chilliness, general malaise, a rise of temperature to 40° C. (104° F.) with congestion of the face and eyes, and dryness of the mouth and lips.

The initial pyrexia persists for 3–4 days and is associated with drowsiness, prostration, and generally with enlargement of the spleen. There is the usual rapid fall of temperature at the crisis, often associated with collapse, and which responds to injections of adrenalin.

The periods of apyrexia and relapse correspond closely to those of the Central African form. After four attacks the disease apparently comes to an end spontaneously. The Spanish type of relapsing fever does not seem to be associated with secondary anaemia, as in the other forms, though there is generally a leucocytosis of 14,000 to 26,000 per c.mm. during the attacks. Herpes labialis is common, and the urine often contains bile at the crisis. Enlargement of the cervical lymphatic glands is said to occur. Acute subarachnoid hæmorrhage as part of a hæmorrhagic state has been recorded by Dewar and Walmsley (1945).

As in *S. duttoni* infections nerve complications have been noted. Facial paralysis has been seen in about 3 per cent. some six weeks after the last relapse, and iritis is noted in about the same proportion of cases. In the campaigns in the Libyan Desert, Bodley Scott (1944) reported nerve-complications in 22 per cent. This spirochaete is neurotropic, so that meningitis, hemiparesis, facial palsy and ophthalmoplegia were recorded. Focal damage leading to lesions of the fifth, sixth and seventh cranial nerves was noted. The cerebro-spinal fluid was under pressure with lymphocytic pleocytosis, increased protein and globulin: spirochaetes could rarely be demonstrated.

The prognosis is usually good. The immunity to this strain of spirochaete appears to last about a year.

V. TICK-BORNE, CALIFORNIAN, CENTRAL AND SOUTH AMERICAN TYPES (*Spirochaeta turicata* and *S. venezuelensis*) present no special clinical features, but resemble in the main Central African tick-fever.

Ocular complications of relapsing fever.—These were studied by Hamilton (1943) in the Middle East. They are thought to be due to the presence of numerous spirochaetes in the ocular blood vessels. Acute iridocyclitis merges into chronic cyclitis with persistent headache. Posterior synechiae develop, which may be broken down by miotics. A gross vitreous exudate is marked. Despite cyclitis and vitreous changes, no choroiditis is observed. Prognosis for vision is good. These complications are specially marked in the louse-borne type. Optic atrophy appears to be confined to *S. duttoni* infections.

Mortality of relapsing fever.—The death-rate is usually below 6 per cent. In a serious form with jaundice, which has been noticed on the West Coast of Africa, the death-rate may exceed 50 per cent. In the feeble and old, death may ensue at the height of the first paroxysm, or from exhaustion as the result of relapses.

Diagnosis.—This fever is most usually confused with subtertian malaria, from which it may be at first indistinguishable on clinical grounds; it may also resemble leptospirosis, enteric, typhus, influenza, dengue, pneumonia, malignant smallpox, and even plague. In South America and West Africa it may be confused with yellow fever. Detection of the spirochaetes with the microscope, or by animal inoculation, is the most reliable method of diagnosis, especially during the febrile paroxysms, and they are readily demonstrated with the dark-ground illumination. At an early stage the relapsing character of the fever is not available as an aid to diagnosis, but at a later period the history of a fever which had relapsed about fourteen days from the onset of the disease should be regarded as suggestive. *Sudden infarction of the spleen may simulate an acute surgical abdomen.*

Wassermann reaction.—A strong pseudo-positive complement-deviation is obtainable, both during the pyrexial stage and in the apyrexial periods between the early relapses, in about 20 per cent. of cases. This apparently applies to all clinical types of the disease and therefore does not necessarily indicate a syphilitic infection. An efficient complement-fixation test has been elaborated by Wolstenholme and Gear (1948), employing as antigen a suspension of spirochaetes (*S. duttoni*) grown on the chorioallantoic membrane of the chick embryo. The test is useful for diagnosis in obscure cases as well as for assessing the effects of treatment.

Treatment.—Careful nursing and dieting are necessary, especially in the African type, and must be maintained after the crisis, when the patient may be ravenously hungry.

(1) **Antibiotics.**—**Penicillin.**¹—Based upon experimental studies on *S. recurrentis* in mice by Lourie and Collier (1944) and later by Eagle and Magnuson, the therapeutic efficacy of penicillin in the treatment of relapsing fever has been established. With full doses of 50,000 units at hourly intervals the spirochaetes disappear from the blood of these animals within 24 hours. The two last named workers estimated the curative dose in man at 25 mega units.

Schuhardt and O'Bryan (1945) have shown that intracranial penicillin therapy cures brain infection in experimental relapsing fever in white rats.

Taft and Pike (1946), in two patients, gave penicillin in doses of 40,000 units every three hours for 60 doses—a total of 2,400,000 units—causing the fever to disappear within 72 hours. There were no relapses.

Greaves and colleagues treated 271 patients with louse-borne relapsing fever in Tunisia with penicillin. Total dosage was 480,000 units for adults and 360,000 for children. All showed a rapid clinical recovery. Ingranham and Lapenta (1946) injected 52 patients with the louse-borne type intramuscularly every three hours till a million units had been reached. No relapses occurred.

Muwazi (1946) treated 37 patients with "tick fever" (*S. duttoni*) in Uganda—a form which proved more resistant to penicillin. Eighteen received a total dosage of 9 mega units of penicillin. The Egyptian strain of *S. recurrentis* has shown itself particularly amenable to penicillin.

Streptomycin.—Narain and Kalra have treated 18 patients in Kashmir with streptomycin daily in two divided doses of 1 grm. each at intervals of 3–4 hours for two consecutive days. Treatment began after the last paroxysm. The results were equally good in all cases. Streptomycin cured the two who did not

¹ Strains of *S. persica* are resistant to penicillin and to salvarsan, but are susceptible to aureomycin and terramycin.

respond to salvarsan. Levaditi and others have shown that streptomycin prevents residual brain infections in mice.

Aureomycin is also specific. Gilchrist gave aureomycin by the mouth in 0.5 grm. every six hours for six doses. In four the blood was free from spirochaetes after one dose, in the other four after two. Apart from initial rise of temperature and rigors in a few cases the fall of pyrexia was dramatic. Aureomycin has an action upon spirochaetes in mice.

Terramycin.—Berks and Goodwin (1950) working with *S. duttoni* in mice found it to be 40 times as potent as penicillin. Adler and colleagues (1952) with *S. persica* in rats found that a dose of 20 mgm. per kg. cleared the blood of spirochaetes in two hours.

Gefel and Rubenow (1952) conclude that the tick-borne relapsing fever *S. persica* in Israel is resistant to arsenicals and penicillin, but that terramycin (oxytetracycline) and aureomycin are specific. In 7 cases terramycin was given—2 orally, 4 intravenously and 1 intramuscularly—with success. Parenteral treatment consists of 0.5 grm. terramycin daily for 5 days. In all these cases the reaction was rapid and the temperatures dropped within twenty-four hours. This has been confirmed by Adler.

(2) *Salvarsan*.—Salvarsan and its allied preparations are specific when injected intravenously in doses of 0.3 grm. to 0.9 grm., according to the age of the patient and the severity of the case, the dosage being reckoned as 0.01 grm. for each kilogram of body-weight. After a short aggravation of symptoms a crisis takes place with disappearance of spirochaetes from the blood and, in the majority of cases, recovery. Should relapse occur, a second injection may be given. Of the salvarsan (arsphenamine) compounds, undoubtedly novarsenobillon is the best; neosalvarsan, luargol, arsaly, kharsivan, galyi (0.35 grm.) and salvarsan are useful in a descending order of merit, and sulphoxyl-salvarsan (Höchst) has given good results. The last mentioned, as also sulphostab (Boots) in doses ranging from 0.3 to 0.6 grm., have the additional advantage that they may be given by the intramuscular or deep subcutaneous routes. Evidence shows that salvarsan is most efficacious in the pre-critical period—that is, when the temperature is on the rise, directly the diagnosis has been made; relapses are apt to occur if it is given whilst the temperature is *on the fall*, or during the apyrexial period; this is especially true of the Central African type, some cases of which appear to be resistant to salvarsan treatment. If it is not given in the first attack, it should be withheld until the first relapse, and then injected on the rise of temperature. It is generally agreed that salvarsan ought not to be injected when the crisis is imminent. A very grave reaction, due to the great destruction of the spirochaetes and the liberation of their toxins, with corresponding aggravation of the symptoms, or, it may be, fatal collapse, is apt to ensue. On the other hand, the great majority of otherwise healthy patients recover from most forms of relapsing fever without any specific treatment, although convalescence may be prolonged. Albuminuria does not constitute a contra-indication to salvarsan treatment.

Arsenic-resistance is rapidly acquired by these spirochaetes, so that Moretti and others who studied this problem found that arsenical compounds, which are efficacious in the earlier stages of relapsing fever, may be ineffectual if a prolonged period (say of 100 days) is allowed to elapse between experimental infection with the spirochaete and the administration of the drug.

(3) *Subsidiary methods*.—The collapse and fall of blood-pressure with sub-normal temperature which follow the crisis have to be counteracted by strychnine, brandy, intrarectal douches of hot salines, and by injections of adrenalin and ephedrine. Vitamin K is indicated for the hæmorrhages.

Prophylaxis (see Table III).—In the louse-conveyed forms of relapsing fever prophylactic measures are necessarily aimed at the destruction of lice and their eggs by all measures known to sanitary science—often a matter of very considerable difficulty when dealing with large groups of native porters or labourers, especially during the rainy season. Disinfestation is performed by superheated steam in a portable Thresh's disinfector, or in specially constructed cars in a disinfecting train, the superheated steam being supplied by the locomotive. Garnham has found that DDT mixed with powdered kaolin constitutes the best method of disinfecting native clothing. (For recent measures of louse destruction, see p. 860.)

In the African form, prophylactic measures are much more difficult, and necessitate intimate knowledge of the habits of *ornithodoros*, which does not live on the body of its victim, but emerges at night-time from the native houses to feed on blood. It is also found on the veld, living in the burrows of the wart-hog, but as a rule it is only met in numbers in the vicinity of old camping sites. The tick itself is very difficult to destroy, but can be controlled by gammexane (B.H.C.).

The following rules are necessary :

1. Avoidance of native houses, most of all at night-time—especially those situated on much-frequented routes. Bedsteads of native manufacture should also not be used. Camps should be placed as far distant as possible from native villages. Caves may harbour infected *ornithodoros*.
2. Avoidance of much-frequented ground for camping sites ; *ornithodoros* can exist without food for years. Sleeping on the ground should not be practised unless absolutely necessary, and only when well protected by a mosquito-net. A night-light is recommended to scare away the ticks. Blankets should be carefully inspected before retiring to rest.

Native huts should be so constructed that a space of 8–10 in. intervenes between the walls and the ground. Mud and rubble buildings are inadvisable ; floors should be raised, and made of cement. A deep trench dug round a building and filled with wood-ash has been found effective in excluding ticks. A solution of pyrethrum in white oil (0·18 per cent.) has been found an efficient insecticide for *O. moubata*, applied either directly to the ticks or to floors or bedsteads (see Chapter LII for effect of DDT and gammexane).

Children especially act as a reservoir of the spirochætes and the ticks feed upon them.

Prophylactic inoculation.—Attempts to immunize the inhabitants of an infected district have been undertaken by Russian workers with a vaccine composed of a mixture of cultures of the original and relapse strains of *S. recurrentis*, incubated at 37° C. for three days and subsequently kept at room temperature for 14–16 days until they had lost their virulence. Each man received 1·0, 1·5, and 2·0 ml. at three days' interval. A week after the last injection the blood was found to contain spirochætolysins against both original and relapse strains. The results showed that it was possible to produce immunity by inoculation of dead spirochætes.

TABLE III

	Epidemic Louse Relapsing Fever	African Tick Fever	Other Tick Fevers
<i>Vector</i> ..	<i>Pediculus humanus</i> .	<i>Ornithodoros moubata</i> .	Other species of <i>Ornithodoros</i> .
<i>Haunts</i> ..	Human body and clothes.	Floors, cracks, court-yards.	Rodent burrows.
<i>Transmission</i>	Crushed lice: not hereditary.	Coxal fluid, faeces; hereditary.	In some cases doubtful; hereditary.
<i>Reservoirs</i> ..	Man.	Probably man only. Maybe mice or shrews.	Rodents, squirrels and other animals.
<i>Biology</i> ..	<i>Pediculus</i> feeds only on man; short-lived.	<i>O. moubata</i> feeds mainly on man; lives for months or years.	Species of <i>ornithodoros</i> feed on animals; occasionally on man; lives for months or years.
<i>Disease type</i> ..	Epidemic.	House disease.	Sporadic.
<i>Control</i> ..	Louse control. D.D.T.	Destruction of buildings. Concrete dwellings. Gammexane. Pyrethrum in oil.	Difficult; based on habits of normal hosts or ticks. Gammexane.

Spirochaeta (Borrelia) latychevi, Sofiev. A new species of spirochaete of man has been described by Baltazard and colleagues (1954) in the Meshed province of Persia. The fever that it produces is slight and the infection lasts at maximum 60 days. The spirochaete has a low pathogenicity and does not give rise to any neurological complications. It is suggested that the merion (*Meriones libicus*) is the reservoir. It is transmitted by a small ornithodoros—*Ornithodoros tartakowskii*.

Therapeutic relapsing fever.—Sparrow (1955) has studied the numerous strains of *S. recurrentis* used in the treatment by scarification of mental patients in Tunisian hospitals. The incubation period in them is 4–7 days; duration of first attack 5–7 days. The second attack was shorter than the first. Attempts to reinfect patients after an interval of 2–10 months after the first attack were negative. In treated patients reinfection was obtained after intervals of 6 weeks to 8 months. Moroccan strains were transmitted by ticks, but the therapeutic effects were not so satisfactory as the temperature produced was lower.

For a description of the ticks and their habits, see p. 1027.

CHAPTER VIII

THE LEPTOSPIROSES

WEIL'S DISEASE (AND SEVEN-DAY FEVER)

Synonyms. Icterus Gravis; Spirochætosus Icterohæmorrhagica; Mediterranean Yellow Fever; Griesinger's Disease; Odan-eki (Japanese).

Definition.—A fever, especially found in sewer workers, caused by *Leptospira icterohæmorrhagica* and its varieties, associated, though not invariably, with jaundice and enlargement of the liver. The natural reservoir of infection is usually the rat (*Rattus rattus*, *R. norvegicus*) and field mice (*Microtus montebellii*). Since the original discovery by Inada and Ido (1915) some 50 separate antigenic types have been differentiated and are known as leptospires. The standard work on this subject is "Leptospirosis in Man and Animals" by J. M. Alston and J. C. Broom (1958).

Geographical distribution.—Formerly thought to be especially prevalent in Japan, but has now been recorded from most countries in Europe. It occurred extensively in the 1914–1918 war in Gallipoli, Salonika, Egypt and France, North African Coast, and Mediterranean area in general. It appears to be specially common in Holland and Germany. In West Africa it is endemic in the Congo (near Lake Kivu), French Equatorial Africa, Sudan, Abyssinia. In the Western Hemisphere it has been reported from the United States, Peru, Brazil and Argentine, and British Guiana. Epidemics have been reported in the Andaman Islands, Indonesia and Malaya. There are no records from the Sudan and South Africa.

The disease in the tropics is specially virulent. In Europe it is said to be commoner in summer-time in Holland, where Schüffner observed 451 cases in ten years; it is specially prevalent in the south and in Rotterdam. The Editor, in 1922, recorded a case from immersion in the Thames; others have been observed in Scottish coal-mines (Buchanan), and in Aberdeen. In 1934 it was shown by Fairley, Alston and Broom that Weil's disease is by no means uncommon in the sewer workers of London, and this was soon confirmed in Liverpool and other cities. It is also not infrequent in canal workers. In 1944 an outbreak was recorded amongst British troops in Normandy which persisted from the middle of July to the end of September.

Epidemiology and endemology.—In Japan the disease has a definite seasonal incidence, occurring, as a rule, most frequently in the months of September to November. The organism is found as a harmless commensal in the kidneys of wild rats and mice, and is excreted in their urine. The disease is therefore usually endemic among farmers and miners

who are exposed to wet soil and water conditions. In the Andamans, leptospirosis is prevalent during the South-West Monsoon, and confined to adult males engaged in outdoor occupations.

In some cases water appears to be the source of infection, as first shown by the Editor in 1922. Epidemics have been recorded among soldiers in Italy and in Germany after bathing in certain river pools. It is known that spirochaetes of the leptospira type are widely distributed in water, some of which have been proved pathogenic to guinea-pigs (Zuelzer).

In Holland Schüffner showed that the highest incidence is amongst those whose occupation brings them near canals, and especially those who have fallen in by accident.

Schüffner demonstrated that the non-pathogenic *L. biflexa* (Zuelzer) occurs in any kind of water, but that pathogenic *L. icterohæmorrhagiae* can be demonstrated by immersing experimental guinea-pigs in suspected pools.

Slime fever (*L. grippityphosa*) is an abortive form of Weil's disease prevalent in Germany and Russia, where it is often acquired during bathing. The attack begins with a rigor and a rise of temperature to 104° F. "Field fever", or *Maladie des porchers* in Savoy, in pigs and man, is due to *L. pomona*.

Schüffner and Uhlenhuth described outbreaks of infection with *L. grippityphosa* in Holland and Germany, and the part played by voles (*Microtus arvalis*). Children are mainly infected during play in the fields, where they collect these rodents and are frequently bitten by them. In the Kivu district of the Congo van Riel has found a local rodent (*Arvicanthus abyssinicus*) infected with *L. grippityphosa* and *L. bataviae*.

Annual outbreaks of leptospirosis of great severity were reported in 1933 and 1934 in Queensland. These occurred among sugar-cane cutters and farmers, especially after prolonged rainfall, the infection having entered through scarifications of arms and legs. A native species of rat (*Rattus culmorum*) appeared to be the carrier of the infection. A new leptospiral serotype—*Leptospira celledoni* has been isolated from Queensland and six similar strains from Malaya (Broom and Smith, 1936). Agglutination titre reached only 1:300 at the end of the fourth week. In 1934, Davidson, Campbell, Rae and Smith described an epidemic of nineteen cases in Aberdeen, chiefly among fish workers. The patients were handling fish in rat-infested premises, the floors of which became covered with slime and offal. The hands are traumatized in doing this work, so that the infection can enter. Depilated guinea-pigs were easily infected with water obtained from this source. Leptospirosis has, therefore, become an "occupational disease."

The disease occurs in dogs, especially hounds, in which it is known as "the yellows," and has been recognized in the fox, especially the silver variety, and in leopards, especially when fed on rats. Stuart (1946) and others have shown that healthy dogs harbour both *L. icterohæmorrhagiae* and *L. canicola*. Broom and MacIntyre (1948) have proved that in 27 per cent. of healthy dogs the serum agglutinates leptospiræ, and that the great majority of the positive results are due to *L. canicola*. Canine epidemic gastritis and canine typhus ("Stuttgart disease") is identical with it. Others have been recorded in Austria, Denmark,

California, Norway and in England where an increasing number of cases has been identified by Broom (1948) and colleagues. "Canicola fever" has therefore become increasingly common in Britain.

In Malaya the first case was found by Fletcher in 1925 and in 1927 Symonds, veterinary officer in Kuala Lumpur, recognized the disease was identical with the "yellows" in dogs.

Coghlan, Norval and Seiler (1957) have described *canicola* fever in man through contact with infected pigs. There were five cases which were diagnosed on clinical and serological evidence and all were piggery workers on a farm near Edinburgh. The pigs which harboured *L. canicola* show hardly any noticeable symptoms. Antibodies were present in 61 per cent. of pigs and leptospiræ were found in their urines. Leptospirosis occurs in hedgehogs. Reported from Russia in 1951, it has been found in Poland, Czechoslovakia, Roumania and in Scotland (Broom). *L. canicola*, *L. grippotyphosa* and *L. bratislava* have been isolated.

Alston and Broom (Leptospirosis in Men and Animals. Monograph, 1958) state that there are now 50 named types of leptospira. Of these some 39 have been antigenetically determined. They tabulate the degree of severity of disease caused by the principal serotypes as follows:—

- I. Most frequently icteric—most severe:
L. icterohæmorrhagiae
- II. Less frequently icteric—less severe:
L. andaman A *L. autumnalis*
L. australis A *L. batavica*
L. australis B *L. pyrogenes*
- III. Usually anicteric—benign leptospirosis:
L. ballum
L. canicola *L. hyos*
L. grippotyphosa *L. pomona*
L. hebdomadis *L. sejroe*

Ætiology.—*L. icterohæmorrhagiae* is found in the blood, urine, cerebrospinal fluid and sputum. It is a spiral filament with wide flexures, the

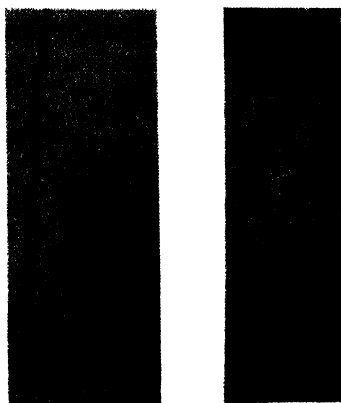


Fig. 40.—Microphotograph of *Leptospira icterohæmorrhagiae*.
× 7,000. (Dr. J. C. Broom.)

individual spirals being in close apposition (Fig. 40). The largest forms attain a size of 20 μ by 0.25 μ , the average length being 6–12 μ .

It is now generally agreed that the organism is identical with *L. icteroides*, the organism described by Noguchi in yellow fever.

The minute structure of *L. icterohæmorrhagiæ* by the electron microscope is described by Swain, Fulton and Spooner. The organism consists of a cylinder of homogeneous protoplasm wrapped round a single axial filament, both enclosed in a thin membrane. The axial filament is straight and does not conform to the waves of the organism.

The organism may be demonstrated by the dark-ground illumination, but is so extremely active that its movements can only be seen with difficulty. According to Fletcher, it is most readily demonstrated in blood-films by Fontana's method. Although easily demonstrated in guinea-pig it can be found in human blood only after prolonged search. In microscopical sections of infected organs the leptospiræ show up well with Levadé's method of silver-nitrate impregnation.

The organisms exhibit rapid movements; when free, one end is extended and straight the other semicircularly hooked, so that they progress in the direction of the straight portion and appear to be propelled from the rear by the rotating hook.

This parasite was cultivated by Noguchi on solid media, such as blood-agar or gelatin. According to Fletcher, it grows readily on agar impregnated with immune serum, but is agglutinated thereby in a peculiar manner. The culture medium used by Dutch workers consists of tap-water 1,500 ml., Witte's peptone 0.15 gm., Ringer's solution 300 ml., and Sørensen's solution of pH 7.2. The final reaction of this peptone medium should be between pH 6.8 and pH 7.2. Three millilitres are placed in a small tube and sterilized, and 3 ml. of rabbit's serum is added. The tubes are then heated to 56° C. for thirty minutes and incubated at 37° C. overnight; thereafter at 30–32° C. A small amount of hæmoglobin improves growth. Leptospiræ are seen by the dark-ground illumination on the fifth or sixth day. Stefanopoulo, Morrow and other workers have cultivated *L. icterohæmorrhagiæ* on the chorioallantoic membrane of the chick embryo and they can survive for several days in whole clotted blood.

Strains of organism isolated in Queensland by Clayton and Derrick differ from those of European origin. They are named *L. australis* A and B; and a third described by Broom and Smith (1956) is known as *L. celledoni* (see p. 190).

There is some divergence of opinion on the advisability of regarding serological races of leptospira as distinct species. Methods of differentiation, such as the Rieckenberg reaction, are considered by some to be too delicate and uncertain. Antigenic types are now separated by serological methods and are referred to as *serotypes* and assembled into *serogroups*. Serological tests provide an indication of the antigenic composition of micro-organisms. Therefore the serological characters may be utilized as a basis of classification. The individuality of *serotypes* is established on the evidence provided by cross-absorption tests.

The common natural reservoir of the leptospira appears to be the rat, in which it occurs in the fæces, urine, and kidneys, though it has not yet been demonstrated in the blood. The disease is believed to have been originally epizootic in rats, but these animals have now become tolerant. The leptospira has been demonstrated in 82.4 per cent. of wild rats in Japan, in 56 per cent. in Holland (Schüffner), less frequently in France, Tunis and Algiers, and in 4 per cent. of sewer-rats in London. In the United States the proportion varies from 4 to 83 per cent. *L. icterohæmorrhagiæ* has been demonstrated by Buchanan in the zoogloea-like "roof-slime," which constitutes a source of infection in certain coal-mines in Scotland. It has also

been found in the green slime of sewers in London by J. M. Alston. Probably in this case the portal of entry is through skin abrasions, and guinea-pigs have been infected by rubbing cultures, slime or suspected water through the skin. Water again may be a source of infection, especially when it comes into contact with the bronchial epithelium, as by diving and swimming the "crawl stroke" (Schüffner). In Sumatra it is thought that native dogs may constitute a reservoir, as Kouwenaar and Wolff found 6 per cent. of dogs in Medan to be carriers, and the organisms were proved to be present in the kidney tissues. Occasionally, human cases of infection by *L. canicola* have been found in Holland and in England too (Laurent, Broom, and colleagues). The dogs may be quite normal or present symptoms. Human cases from the bites of infected rats have also been reported.

Pathology.—The liver is invariably increased in size, and may weigh 100–150 oz. The gall-bladder is generally half-filled with brown or greenish-brown bile. The various microscopic lesions are reducible to three main types. In the first there is little destruction of the parenchyma or intercellular tissue; the second is characterized by extreme cellular degeneration; in the third there is a localized destruction of glandular tissue. The fatty degeneration of the liver in Weil's disease is moderate and not so advanced as that seen in acute yellow atrophy. The leptospiræ can be demonstrated among the cells in large numbers by Levaditi's method. There is remarkable similarity between the pathology of this disease in man and in infected guinea-pigs. In the liver the cells appear to be killed individually: not in bulk. The spleen may be enlarged and the glandular substance soft and diffuent (about 12 oz.). A generalized enlargement of the lymphatic glands, especially at the hilum of the liver, with hyperplasia and multiplication of the mononuclear cells, has been noted. Hæmorrhages occur in the kidneys, mostly in the intertubular tissues; later in the disease the microscopic picture may resemble that of early interstitial nephritis, and leptospiræ may be demonstrated in great profusion. The cells of the convoluted tubules are specially attacked. The renal lesions caused by *L. canicola* have been studied by McIntyre and Montgomery, who have shown that the intense cellular infiltration, limited to the boundary zone, implies the operation of the renal-shunt mechanism of Trueta. The picture is similar to that found in blackwater fever and the crush syndrome. Blood escapes into the glomerular capsule and down the lumen of the tubule. A characteristic type of non-inflammatory degeneration affecting small groups of voluntary muscle, particularly the gastrocnemius, has been described. The cytoplasm loses its cellular detail and striations disappear. There is said to be a reduction in the hæmoglobin and polymorphonuclear leucocytosis of 10,000 or more. There is also a reduction in the number of blood-platelets to 10,000 per c.mm. (normally 300,000). The coagulation-time of the blood is increased to twenty minutes.

Inoculated guinea-pigs and puppies show marked tendency to bleed; hæmorrhages into the lung impart a characteristic appearance, the so-called "butterfly lung," or "butterfly patches."

Symptoms.—Leptospirosis is apt to occur in epidemics, such as those of *L. grippotyphosa*, involving hundreds of agricultural workers which have been reported in Germany and Israel. In N. Italy similar outbreaks in rice workers are due to *L. bataviae*. In U.S.A. infection with *L. pomona*

is widespread in cattle and the cause of bovine abortion. Clinically there are three main types:

- (1) Severe with hepato-renal damage, or Weil's disease;
- (2) Types with meningeal irritation (Swineherd's disease, *L. pomona*);
- (3) Type characterized by abdominal disturbances. *L. grippotyphosa* infections—an excessively severe type in which jaundice is uncommon.

The clinical symptoms can be divided into the first, or *febrile*, the second, or *icteric*, and the third, or *convalescent* stage. Sometimes the curious phenomenon of "*after-fever*" is observed. The *incubation period* in man, as well as in experimental animals, is from six to eight, seldom as long as thirteen days. The *onset* is acute, with rigors, vomiting, headache, diarrhoea, and abdominal pains, which may simulate acute appendicitis. A few hours later, fever ensues, with thirst and very severe general aching of the limbs. There is intense injection of the eyes, which may constitute the earliest and most striking feature and is almost pathognomonic. A distinct network of vessels is seen on the cornea and sclerotics. This reaction is believed to be due to primary invasion of the conjunctiva by leptospiræ. There is also a red plush-like injection of the soft palate, and often herpes labialis, which may be hæmorrhagic. The intense prostration, the almost agonizing muscular pains and aching of the bones, with hyperæsthesia of the calf muscles, as if the muscles were being cut through with a knife, constitute the most distressing features of the illness. The muscles themselves are very tender. The pyrexia is irregular, between 103° and 105° F., falling by lysis in severe cases about the tenth or eleventh day. There is usually a secondary terminal rise of temperature lasting three to nine days, which is associated with excretion of leptospiræ from the urinary tubules. Convalescence is established in the third week, but there is sometimes a short temporary recrudescence of fever ("*after fever*") which is thought to be an allergic phenomenon. Jaundice, which occurs in 50 per cent. of cases, is noted in from forty-eight to seventy-two hours from the onset and may be ushered in by hæmorrhages into conjunctivæ or skin, or even from mucous surfaces. Both icterus and hæmorrhage are ascribed to interference with prothrombin production in the liver. The skin is lemon- or orange-coloured, rarely greenish, pruritus being very frequent. The icterus is probably dependent on disorganization of function of hepatic cells, and is also due in part to hæmolytic icterus following destruction and phagocytosis of red blood corpuscles. The Van den Bergh reaction is therefore almost always biphasic. The jaundice becomes progressively deeper until the ninth or tenth day, but afterwards fades with great rapidity. From the fourth day onwards there may be rashes, morbilliform, erythematous or papular, over the loins, sides of the abdomen and below the scapulæ, symmetrically distributed. A purpuric rash betokens a bad prognosis. Large black hæmorrhagic spots are sometimes seen.

The urine is highly coloured, nearly always containing albumin (which may be fleeting) and bile, and sometimes casts and red blood-corpuscles. The amount is reduced, and the albumin content may be considerable, and usually persists for seven to ten days, after which a trace only may

be found. Bile pigments have been noted in the urine in patients without overt jaundice. The blood-urea is usually raised before the tenth day of the disease, and a secondary rise occurs during the secondary fever. The leptospiræ may be demonstrated in the urine from the tenth day to the twenty-fifth, and may persist as long as 63 days. They can seldom be recovered from the blood after the twelfth day.

Prostration may be extreme. Constipation is the rule, but the fæces contain abundant bile. The pulse is slow in the later stages, and the blood-pressure low. A polymorphonuclear leucocytosis, of 10,000 per c.mm. or over, is present with an Arneth "shift to the left"; later there is an increase in lymphocytes. A high blood-urea of 200-300 mgm. per 100 ml. of blood is usually found, but is not necessarily serious. Renal lesions develop early and too much emphasis is liable to be laid on the hepatic aspect. The liver may be enlarged, but splenomegaly is quite exceptional; the gall-bladder is distended and tender; the lymphatic glands, especially the inguinal and axillary, are often palpable and tender.

The *third* or convalescent stage begins on the thirteenth or fourteenth day with rapid subsidence of the icterus. The patient remains weak, anæmic and emaciated. During convalescence guinea-pigs can still be infected by injection of urinary sediment.

Mild form.—After three or four days, in mild cases, the fever subsides by lysis. Slight or even severe febrile relapses are often seen at the beginning of the third week. Davidson (1937) and Sladen (1939) called attention to "subclinical" forms in those exposed to infection. Mild or anicteric infections usually escape diagnosis.

Varieties.—Typhoidal, uræmic, and meningeal forms—all of great gravity—have been described. In the typhoidal type there may be black vomit, delirium, and muscular twitchings. Insomnia is invariable. In the meningeal type the cerebro-spinal fluid is under pressure, and contains excess of albumin and leptospiræ in large numbers. Murgatroyd described a peculiarly chronic meningeal form in which the leptospiræ were recovered from the cerebro-spinal fluid six months, and from the urine eight months, after the onset of the illness. Mollaret and Erber have found that forms of leptospiral meningitis are comparatively common in France. Transverse myelitis and progressive paralysis have occasionally been reported. Fatal cases are usually associated with paraplegia.

Headache is severe and is associated with vertigo, mental confusion and Kernig's sign. Nystagmus and diplopia, iritis and irregularity of the pupils are common. Skin rashes of short duration are noted. In the cerebrospinal fluid the cell count and protein are increased, but glucose and salt concentrations are normal.

In *L. canicola* infections the disease may be somewhat indefinite and jaundice is rare. Important diagnostic signs appear to be fever, conjunctivitis, appearance of a rash about the fifth day and symptoms of meningeal irritation. Canicola fever should be suspected in all cases of lymphocytic meningitis. In the form known as swineherd's disease caused by *L. pomona*, meningeal irritation is predominant. "Canicola fever" is becoming increasingly recognized and over 70 cases have been diagnosed in England and Wales (Broom). It has been reported from

Scotland (Jol and Sangster, 1951) and from N. Ireland by Kennedy, Crozier and Houston in 1958.

Complications.—Epistaxis, hæmaturia, melæna, hæmoptysis, deafness and pharyngitis have been noted as complications, and also inflammatory ocular changes, such as iritis and iridocyclitis. The secondary fever (after fever) or recrudescence with rigors may occur about the fourteenth or fifteenth day without recurrence of jaundice. During this stage a remarkable pyrexia may develop; in Japan it is seen in 80 per cent., and in Europe in 40 per cent. of cases and may last 14–24 days. The height of the fever is often greater than during the first febrile stage. There are many arguments against the view that this fever is a relapse, as all attempts to infect guinea-pigs with blood have been negative. It is generally regarded as allergic, and due to absorption of toxins. The sequelæ are anæmia and debility. Alopecia usually occurs in convalescence.

The mortality-rate may be fairly high—in the Andaman Islands about 18 per cent.

Diagnosis.—The urine from the fifth to the eighth day gives an intense green reaction when one or two drops of acetic acid are added. Early in the disease, if possible before the third day, the blood should be examined under the dark illumination for leptospiræ, and in doubtful cases should be inoculated into guinea-pigs for confirmation. For this purpose 6 ml. should be injected directly into the peritoneal cavity; citrated blood acts equally well, if not kept longer than twenty-four hours. The diagnosis may also be made, probably with more certainty, from the twelfth day onwards, by injection of the same quantity of catheterized urine. According to Fletcher, the diagnosis is most simply and readily made by direct inoculation of the blood into blood-agar, and subsequent incubation. Blanchard and Lefrou (1922) increased the chances of finding the parasite by triple centrifugalization of the blood. According to Schüffner, one centrifugalization of 10 minutes' duration at 1,500 revolutions is useful in demonstrating leptospiræ, when the plasma is separated from the precipitated red blood-corpuscles and then examined in a thick layer. Sheldon (1945) has drawn attention to the lesions of striated muscle first described by Pick (1917). Loss of striation and vacuolation of the fibres occur early and suggest muscle biopsy as a diagnostic test.

Wolff (1954) used darkground illumination of the blood, preferably using sediment obtained by differential centrifugation which permits immediate diagnosis of leptospirosis in the first few days of illness. Care must be exercised so as not to mistake blood filaments for leptospiræ. "Bathing technique", by immersing guinea-pigs in contaminated water, is employed by Appelman for isolating strains of leptospiræ. Agglutinins and agglutinin-absorption tests are essential tools for identifying newly isolated strains and for analysing antigenic constitutions. Complement-fixation tests are also employed.

An agglutination test with cultures of leptospiræ grown on solid media is much used; it occurs in a titre of 1 in 500, 1 in 1,000, and even as high as 1 in 80,000 (Davidson, Schüffner *et al.*). The specific agglutinins appear in the serum as early as the sixth, more generally about the tenth day of the illness, and persist for as long as twenty-two months.

Postmus (1933) found that this property of the serum may sometimes persist for eight years or longer. In carrying out the test Schüffner used living cultures of leptospiræ, and also cultures killed and preserved in formalin (0.2 per cent.). A small amount of gentian violet may be added to facilitate the reading of the results. One drop of antigen and various dilutions of serum are mixed in squares ruled on a slide, rocked for ten minutes, and then examined on a white background in diffuse transmitted light. On the whole, macroscopic agglutination test is less sensitive than the microscopic. For macroscopic agglutination test antigen is prepared from actively growing young cultures of leptospiræ. The volume of culture added is equal to six times the volume of each dilution of serum tested. The mixture of serum and culture should be incubated for three hours at 37° C., followed by thirty minutes at 55° C. With living leptospiræ agglutination appears only in the lower dilutions, as in the higher lysis sets in, rendering agglutination impossible. The one disadvantage is that the formalin mixture after some weeks is rendered useless by matting together of the leptospiræ into felt-like clots. The agglutination-absorption test was used by Schüffner and others as a means of differentiating strains of pathogenic leptospiræ; by these means he separated *L. canicola* of the dog.

Gardner (1947) uses rich cultures of living leptospiræ. Agglutination is observed with dark-ground illumination. With a 3-mm. loop a loopful of suspension is placed on a slide and 1-mm. loopful of 1 : 10 dilution of serum added to make a dilution of 1 : 100. Preparations are best examined under dark-ground illumination. Care must be taken to avoid auto-agglutination.

The cultures used for the macroscopic agglutination test are obtained on Noguchi semi-solid medium by incubating at 32° C. for 5-7 days; 0.2 ml. of such a culture of actively motile leptospiræ is kept in a water-bath for one and a half hours at 37° C., mixed with an equal quantity of antileptospiral serum and examined by dark-ground illumination for agglutination.

Gardner and Wylie (1946) used formalized serum-water cultures of the organism. For the culture a simple solution of 12 per cent. rabbit serum in glass-distilled water is most satisfactory (copper-distilled water is useless).

The agglutination test with killed organisms is most common for routine diagnosis, but in critical experimental investigations living cultures are employed. Cultures are killed by adding formalin neutralized by pyridine or magnesium carbonate. Most workers follow Schüffner's method of setting up the test in the depression of a porcelain palette using a drop technique and making the range of final dilutions of the patient's serum 1 : 10, 1 : 30 and so on. If the test serum has a high antibody content, agglutination may be incomplete in low dilution (prozone effect).

Gæhtgens elaborated a complement-fixation test. The antigen is a culture of leptospiræ, centrifuged, and the sediment suspended in saline containing 0.3 per cent. carbolic acid.

The centrifuged deposit of urine rich in these parasites may be utilized for an agglutination test in place of a culture, and the diagnosis has by these means been placed upon a scientific, if not on a practical basis. The leptospiræ can usually be demonstrated in centrifuged urine, and may be present up to the sixty-third day, though they generally disappear on the fortieth. Davidson has pointed out that their numbers are somewhat inconstant and they may disappear altogether in acid urine. If negative at first, this test should be repeated every second day up to the end of the third week.

An antiserum specific for the *Leptospira icterohæmorrhagiae* has been

prepared from rabbits, and by this means the identification of the organism has been made possible.

Randall and Cooper (1944) have found that the golden hamster (*Cricetus auratus*) is a test animal for the diagnosis of leptospirosis. Leptospiræ can be seen microscopically in peritoneal fluid withdrawn by capillary pipette 3-4 days after inoculation. Young hamsters, 3-4 weeks old, are susceptible to infection with *L. canicola*, but young guinea-pigs and mice prove comparatively resistant. Injection of centrifuged urine from an infected dog in 9-10 days produces death. This test can be employed for the differential diagnosis of *L. canicola* from *L. icterohæmorrhagæ* infections since the hamsters succumb to both, while guinea-pigs succumb only to the latter. Schlossberger and Langbein (1952) have shown that *L. icterohæmorrhagæ* can be transmitted through *Ornithodoros moubata* and can be demonstrated in its eggs.

From the fifteenth day onwards the immunity reaction may be employed; for this purpose 1 ml. of the patient's serum is left in contact, for fifteen minutes, with several times the lethal dose of the leptospire, and injected into a guinea pig, which does not develop symptoms of the disease, while control animals die.

Differential diagnosis.—The disease has to be differentiated from yellow fever, infective hepatitis, catarrhal jaundice, syphilitic disease of the liver, and the icterus of relapsing fever and of malaria. The fever must be distinguished from that of relapsing and of yellow fever, and the leptospira from *Spirochaeta recurrentis*. On clinical grounds the diagnosis should not be missed, when jaundice, associated with nephritis and nitrogen retention, is followed by headache, muscular pains and scattered hæmorrhages. The difficulty in differential diagnosis between leptospirosis and yellow fever may be realized when it is remembered that the cases studied by Noguchi as instances of yellow fever were, almost certainly, cases of leptospirosis. Faget's sign is not present in leptospirosis (see p. 329).

In fevers such as typhus and cerebro-spinal fever, and in several others in which relapse may occur, including plague, rat-bite fever, and paratyphoid (especially paratyphoid-B), jaundice may be a complication. Other possibilities are lobar pneumonia, portal pyæmia, occasionally, *Bact. coli* septicæmia and Heyd's syndrome which is hepatorenal failure with high blood urea. Both have renal signs and jaundice. Hess' test of venous occlusion is decisive when a petechial rash above the constriction becomes apparent in leptospirosis.

TREATMENT

1. General conduct of the case.—The systematic treatment consists in keeping the patient at rest, flushing out the bowel by repeated small doses of calomel, and intravenous injection of normal saline containing 5-10 per cent. of glucose. Should the nephritic symptoms become severe, intravenous injections of saline or of Ringer's solution, $\frac{1}{2}$ to 1 litre, may become necessary. The urea concentration in the blood must be watched. The diet must be liquid and, if vomiting is persistent, should be given as nutrient enemata. For the pruritus accompanying icterus, anti-histamine compounds are recommended. If anuria develops the

fluid intake, which is reduced to the level of insensible loss, is provided by an emulsion of peanut oil and glucose in water. As uræmia and acute renal failure from the 7th-17th days are the commonest causes of death, dialysis by means of an artificial kidney is advocated by Valek (1959).

2. Penicillin.—From 1944 onwards many papers have been published showing the specificity of penicillin for leptospira infections. The results in man have been based on experimental infections in guinea-pigs (Heilman, Herrell, Hart, Cross, Alston and Broom, 1944-45). Bulmer (1945) found that in man this was the most successful form of treatment, given in 40,000 units with an average amount of 1,125,000 units by continuous intramuscular drip, but it is essential that, to be successful, it should be given early, before damage to the liver or kidneys has taken place. All observers have been struck by the dramatic improvement after penicillin in 36 hours. In adequate doses it appears to shorten the general effects of the disease, as assessed by the duration of fever, but it does not affect the degree or duration of cholæmia as established by the icteric index and van den Bergh test. Therefore penicillin should be injected in all cases of Weil's disease as soon as possible and in high doses. Danaraj (1950) states that in 19 cases, including seven with meningitis with changes in the cerebrospinal fluid, penicillin in doses of 50,000 units was given every three hours for 7-10 days with beneficial effects. Broom, on further analysis, has criticized the results of penicillin treatment.

In recent years some of these more optimistic results have been discounted. Fairburn and Semple (1956) in service men in Malaya had disappointing results with 600,000 units 6 hourly for 5 days. In Queensland Doherty (1956) thinks that penicillin shortens the febrile period. Mackay-Dick and Robinson in European troops and Gurkhas express mild optimism. There were no deaths but 80 out of 84 showed a mild Herxheimer reaction which expresses good response to treatment. The need for early institution of therapy deserves great emphasis. More recently *procaine penicillin* (distaquine) ampoules of 3 mega units, requiring suspension in distilled water, is advocated as more suitable for leptospirosis.

Other antibiotics.—Terramycin and aureomycin offer the best chances of success when penicillin fails, provided they are given in the first few days of the disease. Chloramphenicol is useless (Van Theil, 1957).

Prophylaxis.—Prophylaxis manifestly consists in sterilizing the faecal and urinary discharges of the patients, and in waging war against the rat, the natural host of the parasite, and carefully guarding against its access to food. Swimming, especially the "crawl stroke," in pools or rivers known to be the source of the disease should be avoided. Sewer workers must protect themselves against abrasions. Noguchi prepared a vaccine of killed cultures of leptospire which he used for prophylactic inoculation in Japan.

Seven-day fever or autumn fever is a short fever, due to *Leptospira hebdomadis* and *L. autumnalis*, occurring epidemically during the summer months, especially in Japan (Fukuoka), characterized by sudden invasion, severe headache, pains in the back and limbs and pyrexia of a peculiar saddle-back, or occasionally of a continued type, lasting from six to seven days and associated with a relatively slow pulse.

The home of the disease is Japan and Okinawa; it is found in China (Shan-si), and also in India, the Dutch East Indies and Australia, especially in dairy farmers.

L. hebdomadis and *L. autumnalis* resemble *L. icterohæmorrhagicæ* closely, but can be distinguished by serological reactions. They are present, though in small numbers, in the blood-stream during the pyrexial period, may be demonstrated by Giemsa's stain or by the dark-ground illumination, and are readily cultivated by Noguchi's method. The chief channel of elimination is kidneys and urine.

The short-eared field-vole (*Microtus montebelloi*) appears to be the normal host of the leptospire in Japan, and the organism can be detected in the kidneys and urine of 3.3 per cent. of these animals, which can convey the disease by their bite. The endemic area of prevalence of seven-day fever corresponds with the distribution of this vole in Japan. Other subsidiary hosts are *Apodemus agrarius*, *A. speciosus*, and *Micromys arvalis*.

Microtus, sometimes termed a field-mouse, is really a stump-tailed field-vole, and is common in country districts in Japan. It burrows in the ground and feeds on roots and grain in much the same way as other small rodents.

The blood of convalescents from seven-day fever contains specific immune and leptospiracid bodies and, when injected, together with a culture of the organism, into the peritoneal cavity of a guinea-pig, gives a positive Pfeiffer reaction. Young guinea-pigs are susceptible to inoculation with the blood of patients, and with cultures of the leptospire; they may also be infected *via* the skin or *per os*.

The symptoms resemble those of Weil's disease but are much milder and are non-icteric.

Diagnosis and treatment are the same as for Weil's disease.

CHAPTER IX

RAT-BITE FEVER

Synonyms. Sodoku—so (rat), *doku* (poison); Sokosha (Japanese); Cat-bite Disease.

Definition.—An acute febrile disease caused by *Spirillum minus* (*morsus-muris*), inoculated into man by the bite of an infected rat (sometimes also cat and ferret) causing a local disturbance at the site of infection, followed by a general fever, with a tendency to relapse and, in some cases, a cutaneous eruption.

Geographical distribution.—Rat-bite fever appears to have a wide-spread distribution, but is especially common in Japan. Cases have been reported in Great Britain by Horder, Low, Atkinson, and Joeke, and in the United States, Germany, Italy, Australia, and East Africa.

Ætiology.—*S. minus* (*Spirochaeta m. muris*; *Leptospira muris*) is a short, squat spirillum differing greatly from spirochaetes, at any rate in the human body. It measures 1.5–6 μ in length; the pointed extremities are continued into one or more flagella; including this, the total length may be 15 μ . (Fig. 41.) The curves are regular, and generally number three or four, or even six or more. It is difficult to demonstrate in the blood in the living state, even by the ultra-microscope, but it may be seen in the exudate in the neighbourhood of the bite, and in the juice from the superficial lymphatic glands. By this magnification fine flagella appear to clothe the body of the organism.

In the living state the organism, under the microscope, moves rapidly like a vibrio, by lashing movements of the flagella; the body itself is held rigid, and in this manner the movements can be readily distinguished from the vibratile motions of the true spirochaetes. This fact, together with a certain amount of doubt regarding its method of multiplication, has led to some controversy on its systematic position. The presence of the spirillum can be easily verified in suspicious cases by inoculation of white mice with any of the material in which it can be seen. Next to mice, white rats, guinea-pigs and monkeys (*Macaca*) are most susceptible. The spirillum can also persist in the blood of dogs without giving rise to any obvious symptoms. In mice, Ozeki has shown that the infected animals can be recognized within one or two months after infection by the loss of hair on the belly, chest and the nasal line, including the eyes and ears. Usually, however, experimental animals survive. The organisms appear in the bloodstream about seven days after inoculation, and persist for several months. The disease can be transmitted by the brown rat (*Rattus norvegicus*), the black rat (*R. rattus* and *R. alexandrinus*, *R. r. kijabius* (Heisch)), the bandicoot rat (*Nesokia bandicota*), the ferret or cat.

In Calcutta 2 per cent., in Venezuela 10 per cent., in Amsterdam 1 per cent., and in Toulon 18 per cent. of rats have been found infected. *S. minus* has not been found in the rodent's saliva, but the transfer seems to take place by a breach in the tissues through which the organism escapes, and is thus inoculated into the bite wound.

The organism resembles, and is probably identical with, *S. laverani* and *S. muris*, which have been found in the blood of rats and mice in various parts of the world. Levaditi stated that in mice this infection is hereditary. Saisawa and Taise have shown that the spirilla can be found in large numbers in the peritoneal fluid of mice, and when these animals

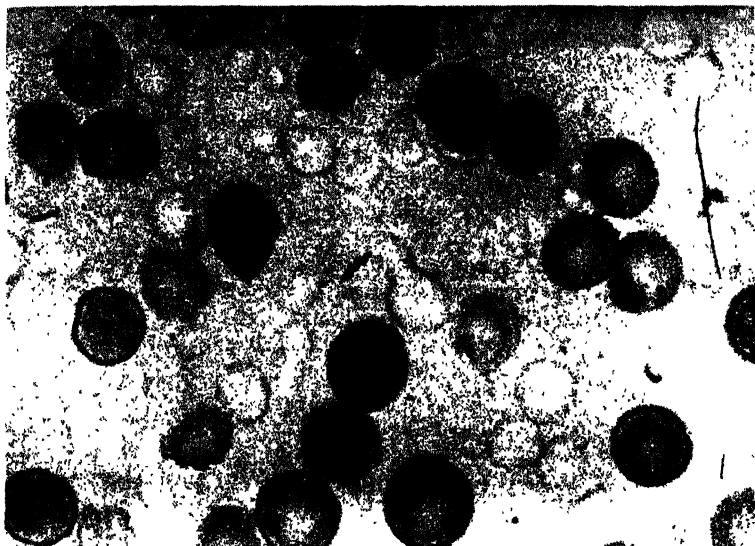


Fig. 41.—*Spirillum minus* of rat-bite fever in mouse. $\times 2,500$.

are treated with small quantities of neosalvarsan, the organisms persist in the brain and in the spleen. Like the true spirochaetes, they have the power of forming remarkable agglomerations, sometimes forming balls 40–50 μ in diameter. Under the dark-ground illumination, these clumps move like a rolling ball.

Joekes succeeded in cultivating *S. muris*, which he found in 25 per cent. of the wild rats in London, by using an inspissated horse-serum slope, as employed for the diphtheria bacillus, over which is poured Vervoort's medium (1 per cent. peptone to which are added 3 c.c. of normal phosphoric acid). Primary culture is obtained by inoculating the medium with blood from an infected guinea-pig and incubating at 37° C. Subcultures are easily maintained in 1 per cent. glucose broth.

The immunity conferred on man and animals by an attack of this fever is permanent, and protects, apparently, against all other organisms of the same type that have been procured from various sources.

Although the general belief is that *S. minus* is the cause of rat-bite fever, it is necessary to state that there are some cases from which *Streptobacillus moniliformis* (*Actinomyces muris*) can be isolated on special media. In the United States it has been found that infection of wild rats with *S. moniliformis* is much commoner than with *Spirillum minus*. By some this is still considered to be the etiological agent.

S. moniliformis (*A. muris*) first isolated in 1914, was shown by Parker to be

responsible for a milk-borne epidemic, "Haverhill fever." It is recognized in the U.S.A. that there are two rat-bite fevers, and that the one due to this organism is curable by intramuscular injections of 200,000 units of penicillin and streptomycin; one case (1948) is reported from Edinburgh from a bite of a laboratory rat by Lominski, Henderson and McNee. The latest work on this organism is by Waterson and Wedgwood (1953).

The differentiation of these two forms is summarized by Witzberger and Cohen (1944) as follows:—

	<i>Sodoku</i>	<i>Haverhill Fever</i>
<i>Transmission</i>	Bite of rat.	Bite of rat or other animal. Possibly contaminated food.
<i>Incubation period</i>	5-30 days.	1-10 days, average 5.
<i>Wound from bite</i>	Apparent healing, followed by chancre-like ulceration.	Heals promptly.
<i>Lymph glands</i>	Regional lymphadenitis.	Not involved.
<i>Systemic manifestations</i>	(a) Regularly relapsing type of fever. (b) Generalized maculopapular rash. (c) Varying degrees of prostration and debility. (d) Arthritis very rare.	(a) Intermittent, but not regularly relapsing type of fever. (b) Macular, pustular and petechial eruption. (c) Varying degrees of prostration. (d) Metastatic arthritis fairly common.
<i>Laboratory findings</i>	Polymorphonuclear leucocytosis. Secondary anaemia. Kahn test, usually +. Isolation of spirillum by animal inoculation of blood or infected gland. Agglutination test negative.	Same. Same. Negative. Isolation of <i>S. moniliformis</i> by blood culture and from pustules on veal infusion broth enriched with rabbit serum. Agglutination tests with <i>S. moniliformis</i> positive. Serum agglutinates a polyvalent antigen of the bacillus.
<i>Treatment</i>	Responds to arsenicals and to penicillin.	Arsenicals of little or no value. Curable with penicillin.

Pathology.—In inoculated guinea-pigs and white rats swelling of the lymphatic glands and spleen is observed. There have been few recorded human autopsies. Degenerative changes occur in liver and kidneys. In some cases increase of cerebro-spinal fluid and hyperaemia of the cerebral cortex have been reported.

Symptoms.—The *incubation period* varies from one to sixty days, the average being from five to ten days, during which time the wound heals. Then the cicatrix itself, and sometimes the surrounding tissues, become inflamed with formation of blebs and even necrosis. The lymphatics draining the area are implicated, and the glands themselves become swollen and tender. The supraclavicular lymph glands are specially affected (Heisch). The onset of the fever is characterized by rigors and malaise; the temperature gradually rises in three days to a maximum of 108-104° F., and, after a further period of three days, ends in crisis with profuse sweating.

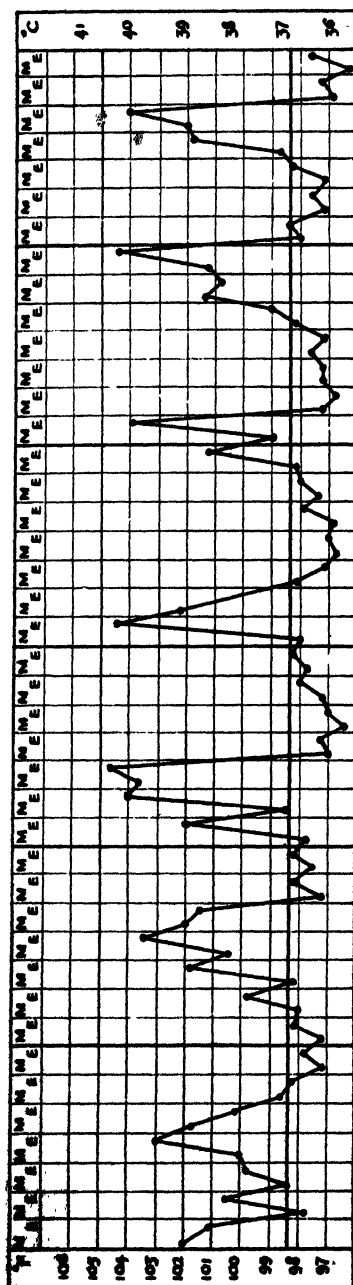


Chart 11.—Rat-bite fever.
periods: relapses. (By permission of London School of Hyg. and Trop. Med.)

After the primary attack a quiescent interval of five to ten days ensues, with subsidence of the local disturbance. One or more relapses (Chart 11), associated with the same symptoms and a characteristic purple papular exanthem, or urticaria, on the chest and arms, have been noted. The eruption is sometimes nodular. With each bout of fever the cicatrix at the site of the original bite becomes inflamed.

In most cases the reflexes are increased; there may be pains in the muscles and joints, hyperæsthesia and œdema of various parts of the body. In some cases arthritis has been reported. The death-rate is about 10 per cent. In fatal cases the end is ushered in by delirium, often lapsing into coma. Some cases subside spontaneously: others go on for months.

As in relapsing fever, the organism can be demonstrated in the blood during the fever only, disappearing during the apyrexial intervals. The serum agglutinates the spirillum in low dilutions. There is an eosinophilia during the paroxysm and a moderate leucocytosis of about 15,000. It is said that the serum in this disease gives a weak positive Wassermann and Kahn reactions.

Diagnosis.—In many cases the diagnosis of rat-bite fever can be fully established from the history, the infiltration at the seat of the bite, the typical temperature curve, the rash, and the effects of the administration of neoarsphenamine or penicillin. This diagnosis can be confirmed either by dark-ground illumination, when spirilla may be seen in the exudate obtained from the site of the bite, or in the serous fluid from the papule, or by Giemsa-stained smears.

It is seldom possible to demonstrate spirilla in a thick blood-film. If a number of relapses have occurred,

probably the best examination to make is for the presence of lytic antibodies. Absolute proof of the clinical diagnosis may be obtained by inoculating the patient's blood, lymph gland, or a piece of excised wound into guinea-pigs and mice.

Savoor and Lewthwaite demonstrated the curious fact that a well-marked rise in *Proteus* OXK agglutinins occurs in the blood of rabbits inoculated with *S. minus*, but in man, as well as in infected monkeys, the reaction is negative.

Differential diagnosis.—This has to be made from the different forms of relapsing and trench fevers, with which the temperature chart has much in common. In tropical countries the possibility of a co-existent malarial infection has to be taken into account. The puffiness of the face accompanying the urticarial eruption may simulate Bright's disease.

The reaction occurring around the site of the scar is apt to be confused with erysipelas or cellulitis.

Treatment.—*Penicillin.*—Lourie (1943) first showed that with penicillin *S. minus* disappears from the blood of experimental mice in 24 hours. These results were later confirmed by Heilman and Herrell (1944). It is equally efficacious against *Streptobacillus moniliformis* (*Actinomyces muris*). Oehme (1950) has reported the cure of rat-bite fever (by bite of water rat) by penicillin which was administered in doses of 25,000 units every three hours till one mega unit had been attained. A crisis occurred 12 hours later with fading of the rash. Sen and colleagues (1954) in Calcutta have reported most favourable results with injection of streptomycin in doses of 0.5 gm. twice daily for 1–4 days. With oral treatment with terramycin (oxytetracycline) the effect was equally good; 2 capsules (0.25 gm.) were given, every 6 hours for one day, one capsule every 6 hours the next. The temperature fell to normal on the first day. Salvarsan and its derivatives act as specifics. As a rule, one injection of neoarsphenamine (0.4–0.6 gm.) is sufficient.

Occasionally the intravenous injection has to be repeated as a prophylactic measure. A cat- or rat-bite should always be cauterized.

As in syphilis, so in rat-bite fever, bismuth compounds appear to have a definite curative value, and in the fungus-infection (*A. muris*) streptomycin is indicated.

Prophylaxis.—Quite obviously, the prophylaxis of this disease, as in plague, rests upon efficient rat destruction. In Manila, for instance, it has been found that the distribution of rat-bite fever and plague are co-extensive and that therefore measures taken against one are in fact effective against the other.

Subsection C.—FEVERS CAUSED BY BARTONELLA AND RICKETTSIA BODIES

CHAPTER X BARTONELLOSIS

(OROYA FEVER AND VERRUGA PERUANA)

OROYA FEVER STAGE (GENERALIZED BARTONELLOSIS)

Synonym.—Carrion's disease ; " Guáitara fever."

Definition.—An acute specific fever, endemic in certain valleys of the Andes, characterized by a rapidly developing anæmia of the pernicious type, irregular pyrexia, and great tenderness over the blood-forming tissues. The organism is *Bartonella bacilliformis*.¹

History.—The first attempt to settle the ætiology of this disease was made by the self-sacrifice of Carrion, a medical student who, in 1885, fatally inoculated himself with the blood from a verruga nodule in Lima. From this experiment Peruvian physicians concluded that the verruga and Oroya fever were different stages of the same disease. Many thousands died of this fever during the reign of the Inca, Huayna Capac.

It is thought that Oroya fever was the disease which proved so fatal to Pizarro's army in the sixteenth century. Bours has recorded that all engineers superintending the building of the Trans-Andean railway contracted fever and half of them died of it. In 1906, out of 2,000 men employed on tunnel work, 200 perished. The monograph of Odriozola (1898) contains a classical account of this.

Geographical distribution.—Between the 9th and the 16th parallels of South latitude, and at an elevation of from 3,000 to 10,000 feet, in certain narrow valleys (quebradas) of the western slopes of the Andes, this peculiar fever is endemic. It is therefore found in Peru, Ecuador, Bolivia, Colombia, and Chile, and probably in Guatemala. A considerable outbreak occurred in the Guáitara Valley in South Colombia, near the Ecuador boundary, in 1936, mainly in the valleys of the Pacual, Juanumbú, Mayo and Sambingo, tributaries of the Rio Patía. Its topical as well as its geographical range is singularly limited ; it is confined to certain hot, narrow valleys or ravines, the inhabitants of neighbouring places being exempt.

It is said that the disease may be acquired when merely journeying through the endemic districts, more especially if the traveller passes the night there. Although out-of-door workers are the most subject, all ages, classes, and both sexes, including infants, are liable.

Ætiology.—During the fever certain rod-like bodies are found in a large proportion of the red blood-corpuscles (Fig. 42), and in endothelial cells of the lymphatic glands. These were noted in 1905² and again in 1909 by Barton,

¹ See the authoritative work, *Infectious Anæmias due to Bartonella and related red-cell Parasites*, by D. Wainman, *Trans. Amer. Phil. Soc.*, 1944, XXIII, Part III. 243-339.

² The first thorough description was given by Odriozola in 1898.

who considered them protozoal; his findings were subsequently confirmed by Strong and other members of the Harvard Commission who termed the bodies *Bartonella bacilliformis*. The organisms somewhat resemble stages of a piroplasm (*Theileria parva*) during its cycle in the lymphatic glands, and similar bodies are found in the blood of normal mice and certain rodents (*Hæmobartonella muris*), which, as Mayer, Borchardt and Kikuth have shown, exist as a latent infection, but which may produce an acute and fatal anæmia, resembling Oroya fever, after removal of the spleen. (The causal organism of dog-anæmia following splenectomy is *Bartonella canis*.) The clinical course of this infection is connected

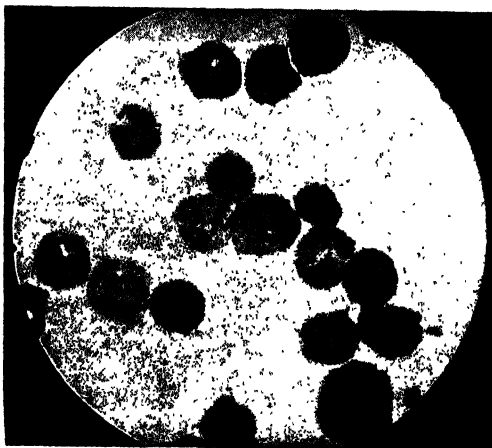


Fig. 42.—Blood smears with numerous *Bartonella bacilliformis* (human Oroya fever). (Kikuth.)

with an endothelial reaction, and the organism is transmitted by rat-lice (*Hæmatopinus*.) From the morphological standpoint, Bartonella and Rickettsia have resemblances. Both are minute, pleomorphic, Gram-negative and intracellular. On account of their peculiar behaviour, *Grahamella*, first described by Graham-Smith in the blood of moles, should be kept apart from *Bartonella* and regarded as a separate genus.

Two forms of *B. bacilliformis* are recognized: one is a rod-shaped, slightly curved bacillary organism 2 μ long by 0.5 μ broad, staining with Romanowsky an intense blue, often in branching forms and in chains, but never crossed; the other is a rounded body about 1 μ or less in diameter, usually oval or pear-shaped, and containing chromatin granules. Some occur singly, or end to end, in pairs or chains. V forms probably represent dividing organisms; Y shaped forms are also not uncommon. They are difficult to distinguish in fresh blood, and show feeble independent movement. Wigand and Peters (1952), using phase-contrast microscopy, have shown that in fresh blood they are feebly motile. When dried films are "shadowed" with palladium, and examined by bright-field microscopy, it is found that the organisms lie in depressions. By electron microscopy flagella are visible, each with diameter of 20 millimicrons, in bundles, up to 10 flagella for each organism.

Noguchi regarded *Bartonella* as a bacillus and succeeded in cultivating it on solid media from specimens of citrated blood sent in "cold storage" from Lima to New York. The organism grows best at low temperature on blood-

agar media. He was so successful in culture of the organisms that he recommended it in diagnosis as preferable to examining blood smears.

Battistini's method of culture is simple. A small drop of blood from the finger of the patient is withdrawn into serum-agar, or Noguchi's leptospira medium. The end is sealed in the flame and the whole placed in the incubator at 28° C. Colonies are visible in 5-6 days. *B. bacilliformis* is also readily cultivated in the allantoic fluid of the developing chick embryo at 25-28° C. The growth is rapid and abundant and the cultivated bodies are 0.6-1.6 μ in length. Weinman and Pinkerton (1938) preferred the agar slant method devised by Zinsser for cultivation of rickettsia. *Bartonella* can also be grown in tissue culture. *Hæmobartonella muris* of the rat cannot be so cultured and differs from *B. bacilliformis* in structure as seen by the electron microscope. The bartonella is an obligatory aerobe and Gram-negative, but stains well with Giemsa. Intravenous injections of cultures into *Macaca* monkeys produce irregular fever and extreme anaemia, whilst the organisms can be demonstrated in the blood-cells. Intradermal injection into the supraorbital tissues gives rise to nodules resembling verruga. In excised nodules *Bartonella* survives for at least fifty-six days at 40° C. Noguchi succeeded in conveying the infection to monkeys by the bites of ticks (*Dermacentor andersoni*), but Townsend in 1913 conjectured that the insect vector was a sandfly (*Phlebotomus verrucarum*). Further evidence incriminating *P. noguchii* and *P. verrucarum* was obtained by Noguchi and others in 1929, and this was confirmed in 1937 by Pinkerton and his colleagues. Insects were collected in a verruga district of Peru and sent in sealed glass tubes to New York. They were then ground up in saline and the emulsion injected intradermally into monkeys. The only insects which showed any evidence of containing bartonella were phlebotomi. *P. verrucarum* (not *noguchii*) is now regarded as the chief vector.

The Neill-Mooser scrota reaction is produced sometimes by inoculation of guinea-pigs with blood of Oroya fever or with cultures of *B. bacilliformis*. If present, it is well-marked on the third day.

Herrer (1953) in blood cultures made from 81 students at San Jan, Peru, found 7 were positive for the organism and one case remained so for four months. The results showed that this method of diagnosis is attended by the best chances of success during the early stages of the infection. It was possible to infect grey squirrels (*Citellus tridecemlineatus*) with comparative ease.

The disease is most prevalent from January to April, when the streams are in flood, the air hot, still, and moist, malaria epidemic, and insect life abundant.

Pathology.—A remarkable feature of this disease is the rapid and extreme blood destruction. In bad cases the blood-count may drop in three or four weeks to 500,000 per c.mm., the picture being that of a pernicious anaemia. There is a marked polymorphonuclear leucocytosis with disappearance of eosinophiles. The red cells are of the megalocytic type.

In addition to the anaemia, marked changes are present in the liver, spleen, and bone-marrow. In the liver, areas of degeneration and central necrosis are found around the hepatic veins. In the centre of the necrotic areas a yellow pigment resembling hæmosiderin is present in abundance. The spleen is invariably enlarged, and also contains necrotic areas with pigment in the pulp, but the Malpighian bodies themselves are not affected. The lymphatic glands contain large macrophage endothelial cells studded with rod-shaped bodies. *B. bacilliformis* commonly occurs in closely-packed masses in swollen endothelial cells, especially those of the lymphatic

glands, spleen, liver and intestines. The lesions in the viscera are considered by Strong to be due to toxins liberated by the parasite. The bone-marrow shows proliferation, necrosis, and marked phagocytosis of the large endothelial cells.

Symptoms.—The *incubation period* of Oroya fever is about three weeks. Its *onset* is insidious and is marked by malaise, soon followed by a rapidly developing pernicious anæmia and an irregular remittent pyrexia, associated with very severe pains in the head, joints, and long bones. The bone pains are probably connected with the disturbances in the hæmopoietic system. Very often the initial fever is like that of malaria and may be the outcome of a superadded infection in a malarial subject. The most severe types resemble fulminating typhus and are known as the "severe fever of Carrion." The liver and spleen are enlarged and tender. The anæmia develops with great rapidity. The death-rate varies from 10 to 40 per cent. of those attacked, the end coming within two or three weeks of the onset of the disease. A terminal delirium is often noted. In those cases which progress to the verruga stage, the fever may last three to four months. Secondary infections with *Salmonella* (*S. typhimurium*) often prove fatal.

Howe has shown (1945) that immunity to this disease is rapidly acquired, but bears no relationship to specific agglutinins in the blood.

Treatment.—*Penicillin.*—Merino reported favourably on two cases, the only ones so far published, with a total of 800,000 units, in doses of 25,000 every three hours. The first four injections were given intravenously, the others by the intramuscular route. The temperature dropped immediately. Payne and Urteaga have used chloromycetin; the fever subsided with 48 hours and *B. bacilliformis* assumed a coccoid form in 24 hours. There was a marked reticulocytosis and a rapid return of the blood to normal.

Urteaga (1955) advocates chloramphenicol as the most specific drug. It terminates the primary infection and is certainly most effective against the grave damages of salmonellosis which is the cause of a high percentage of deaths. The average dose is 17 grm. in divided doses for 5 days. After the first dose the temperature falls to normal within twenty-four hours. It was noted that bacillary forms of the parasite were transformed into coccoid forms before vanishing. Cuadra (1956) also considers that chloramphenicol is the most suitable for *S. typhimurium* which is the common invader.

Prophylaxis.—A prophylactic inoculation with formalized suspensions of *B. bacilliformis* has been introduced by Howe (1948) and has resulted in production of partial immunity in so far that any subsequent attack of Oroya fever is modified.

VERRUGA PERUANA STAGE (LOCALIZED BARTONELLOSIS), OR ERUPTIVE STAGE

Definition.—A remarkable granulomatous eruption confined to certain parts of Peru, Colombia and Ecuador (Montalván and Moral, 1940). It is

associated with hæmorrhages, fever and joint pains. The disease was known to Pizarro, and is described in Prescott's "Conquest of Peru."

Ætiology.—Superficially, the lesions of verruga resemble those of yaws.

As already related, Noguchi demonstrated bartonella bodies in experimentally-produced lesions in monkeys. This work was confirmed by Mackehenie, Weiss, Mayer and Kikuth, who produced nodules in monkeys with human material and demonstrated bartonella bodies within angioblasts or endothelial cells. Verruga is therefore a local connective-tissue infection with *Bartonella bacilliformis*.

Strong's experiments on monkeys showed that graduated inoculation of verruga material induces an artificial immunity. Verruga can be conveyed by inoculation to rabbits and puppies and, according to Townsend, occurs as a natural infection in native American-Indian dogs.

Pathology.—Primarily, the pathological changes consist in proliferation of the endothelium of the lymphatic channels which become obstructed by plasma-cells and fibroblasts, but the structure is much more vascular than that of yaws which it otherwise resembles. The capillary blood-vessels become dilated, so that the granulomatous tumours are vascular, almost cavernous and apt to bleed profusely. A feature of the pathological histology is the formation around the blood-vessels of nodules of angioblasts characteristic of the disease. In the endothelial cells of cutaneous verruga nodules *B. bacilliformis* may be seen in considerable numbers, but distension of the cells is less than that seen in Oroya fever cases (Jiminez and Buddingh). Bartonella bodies may be found in the

blood-corpuses after prolonged search (Mayer), but in monkeys, if the spleen be removed, they multiply exceedingly and produce Oroya fever.

Symptoms.—The period of incubation subsequent to Oroya fever is thirty to forty days, but in those cases in which the initial fever is absent it is at least sixty days. Although verruga is usually a sequel of acute bartonellosis, it may arise spontaneously and independently of Oroya fever. The initial stages are characterized by peculiar rheumatic-like pains, together with fever, the pains being apparently like those of yaws, only more severe. As in yaws, the constitutional symptoms subside on the appearance of the skin lesion. The eruption, like that of yaws (see p. 568), may be sparse or abundant, discrete or

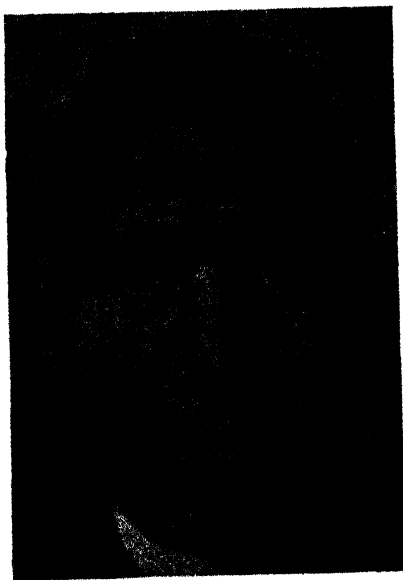


Fig. 43.—Verruga peruana. Millary form from Ecuador. (after Odriozola.)

confluent. As in yaws, individual granulomata may fail to erupt; others may subside rapidly; yet others may continue to increase, and then, after remaining stationary for a time gradually wither, shrink, and drop off without leaving a scar.

The eruption is generally described as of two types, miliary and nodular—the former not exceeding the size of a small pea; the latter, the rarer, less numerous, but consisting of much larger nodular masses. The miliary eruption, as a rule, is found most abundantly on the face and extensor aspect of the extremities, less commonly on the trunk (Fig. 48). A pink macule first appears, which later darkens and becomes nodular. These nodules may be flat or somewhat pedunculated. The verruga artificially produced in monkeys by injection of bartonella bodies is bright cherry pink.

In yaws we find no mention of fungating granulomata in any situation but in the skin. In verruga it seems that these vascular lesions may develop on mucous surfaces—in the mouth, œsophagus, stomach, intestine, bladder, uterus, and vagina. Hence the dysphagia—a common symptom—and occasional hæmatemesis, melœna, hæmaturia and bleeding from the vagina. Relapses both of the fever and of the eruption may occur.

In inoculated monkeys swelling of the lymph-glands is an early and constant symptom.

The nodular eruption is more chronic than the miliary. Individual lesions may grow to the size of a pigeon's egg; they may become strangulated and a source of danger from hæmorrhage. This type does not invade the mucous membranes and is usually confined to the regions of the knees or elbows. It appears in crops and lasts two or three months.

In contrast to Oroya fever, the mortality from verruga is practically nil.

Diagnosis.—The appearances of verruga are so characteristic that it is hardly likely to be mistaken for any other disease. Conceivably, it may resemble the framboesiform eruption of secondary yaws; it may also be simulated by multiple warts, molluscum contagiosum, multiple fatty tumours (Dercum's disease) and, according to Strong, it is closely allied to, if not identical with, Bassewitz's angio-fibroma cutis conscriptum contagiosum. Individual tumours may resemble fibro-sarcoma or angioma. The Oroya and verruga stages frequently coexist.

Agglutination reaction.—Suspensions of *B. bacilliformis* are obtained on media devised by Geiman. Sera from patients were found by Howe to agglutinate the organisms in titres from 1:10 to 1:80 in both the Oroya fever and verruga stages. A co-agglutination is usually found with cultures of *Proteus* OX19, OXK and OX₃. A strong agglutinating serum for testing cultures of *B. bacilliformis* has been produced by intravenous injection of rabbits with living cultures.

Treatment.—Very little is known about the treatment of this condition. Small doses of salvarsan, 0.2 grm. intravenously, have been tried with benefit. From what is already known of the action of penicillin and chloromycetin on bartonella these antibiotics are indicated. When individual tumours begin to ulcerate, or become gangrenous, they should be excised. Dangerous bleeding may occur, and styptics or compresses may be required to stay excessive loss of blood.

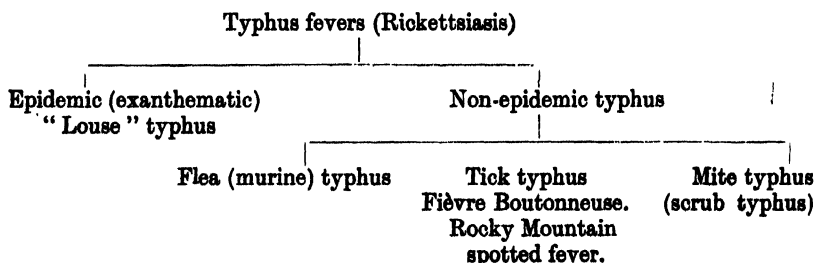
CHAPTER XI

THE TYPHUS GROUP OF FEVERS

Preliminary statement.—Typhus fevers have an almost worldwide distribution, but do not manifest themselves as one definite entity throughout their range. They are divisible into a number of local forms which have become stabilized in type. These forms, or varieties, are probably adapted to local conditions or in some way connected with those arthropod intermediary hosts which convey the rickettsiæ. The student who is interested in the romance of this interesting subject should consult Zinsser's "Rats, Lice and History" (1935).

Classical typhus should be called louse-borne "true" or "exanthematic typhus" and the local varieties be known by their descriptive pseudonyms—murine typhus, scrub typhus, Rocky Mountain spotted fever, *Fièvre boutonneuse*, etc.

The following primary classification somewhat clarifies the situation:



Other forms of tick typhus are South, West, and East African, Indian, South-East Asian, Western Siberian, Northern Queensland.

Ætiology of the group.—*Rickettsiæ* are Gram-negative bacteria-like bodies, usually less than $0.5\ \mu$ in diameter. There are at present eight named species and several varieties. The organism originally named *Dermacentroxenus rickettsii* by Wolbach, first described by Ricketts (1910), and now known as *Rickettsia rickettsii*, is the causal agent of Rocky Mountain fever. The rickettsia of louse-borne typhus was named *R. prowazeki* by da Rocha-Lima (1916) in honour of two distinguished investigators (Ricketts and Prowazek) who both succumbed to the disease, and the latter of whom was the first to recognize their true nature. Topfer (1916) described rickettsia in lice removed from patients suffering from Volhynian fever (trench fever), but this is now known as *R. quintana* (*R. volhynica*). Sellards (1928) distinguished the organism of tsutsugamushi disease in Japan as *R. orientalis* ($=R. tsutsugamushi$, *R. nipponica*). The organism of flea-borne typhus is *R. prowazeki*, var. *mooseri* ($=R. muricola$). The causal agent of *fièvre boutonneuse* is sometimes known as *R. conori*. The rickettsia of "Q fever," *R. burneti* (now known as

Coxiella burneti, Parker, 1949), a comparatively recent discovery by Burnet and Freeman (1935), has a wide range in Australia, North America and Europe, and is of much greater importance than was at first realized. Rickettsialpox in New York is due to *R. akari*.

Trench fever, Q fever and rickettsialpox although classifiable as rickettsias, do not strictly belong to the typhus group.

Rickettsiæ are found commonly in the alimentary tract of blood-sucking and non-bloodsucking insects but, probably, they were primarily parasitic in the cells lining the canal, as is the case with *R. prowazeki*. For instance, *R. pediculi* is an extracellular organism which is an inhabitant of the gut of the louse, is harmless to its host and also to man, resembling *R. quintana* which develops in the same manner and situation.

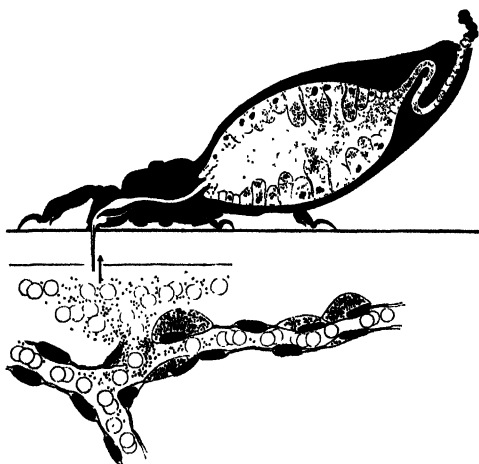


Fig. 44.—The life-cycle of *R. prowazeki* in the louse and the vascular endothelium of man. (Geigy and Herbig.)

The cycle of development of *R. prowazeki* in the louse consists primarily of great multiplication in the midgut, both in the lumen as well as inside the epithelial cells, which become distended. After a few days these rupture and rickettsiæ appear in large numbers in the fæces; this rickettsial invasion killing the louse in about ten days (Fig. 44). The blood of typhus patients is infectious for the louse from early in the disease till the tenth day—occasionally later, even when the patient is afebrile. The disease therefore is conveyed to man by louse fæces through abrasions in the skin, or even through the conjunctiva; possibly also by inhalation. Louse fæces kept dry at room temperature have been proved to be infective for 66 days. There is no hereditary transmission, whilst louse eggs do not contain the virus. A possibility exists that "clean lice" may themselves be contaminated by the excreta of other typhus-infected lice when feeding.

R. prowazeki, var. *mooseri* (*R. muricola*), is normally transmitted from rat to rat by the rat louse (*Polyplax spinulosa*) and by the tropical rat mite, *Bdellonyssus* (*Liponyssus*) *bacoti*. In these insects the cycle is

similar to that already described in the louse. The species of flea mostly concerned is *Xenopsylla cheopis*, but in this instance the infection causes it no appreciable harm. *X. astia* may also act as a vector. In the faeces of the flea rickettsiæ remain alive and virulent for long periods—40 days in the dark and 100 days *in vacuo*. Zinsser and other authorities regarded flea typhus as the original pristine form of human typhus, but this is by no means certain.

The cycle of development of rickettsiæ in ticks follows on much the same lines, but is much more widespread. The rickettsiæ invade the cells and their nuclei; they are found in all tissues, including the ovaries of the female tick, so that the infection is transmitted hereditarily. Rickettsiæ are also found in the salivary glands so that infection is commonly conveyed by the bite of the arthropod. The similarity of the clinical appearances of various forms of tick-borne typhus is undoubtedly close in widely separated geographical regions. In only one particular can they be said to differ—in the absence of a primary lesion in Rocky Mountain spotted fever and its presence in other types.

Zinsser has pointed out the importance of the hereditary factor in tick-transmission as indicating a very ancient condition, producing a mutual tolerance, so adjusted that neither the well-being of the animal reservoir nor of the tick intermediary is impaired.

The mode of transmission of the rickettsia from animals to man, or from man to man, and the relationship of the various forms of typhus to one another can be expressed as follows:

Epidemic louse-borne typhus

Murine Typhus

Man—Louse—Man

Rat { Rat Flea } - Rat.
Rat Louse

Rat—Flea—Man.

Rat—Flea—Man—Louse—Man (possible)

Teutsugamushi. Scrub Typhus (Mite Typhus)

Spotted Fever Types (Rocky Mountain Spotted Fever). "Tick Typhus."

Fièvre Boutonneuse. S. African tick-bite fever

Q Fever

? Rat or Field Mouse—Mite—Man.

Rodents (Gopher)—Tick—Tick—Man.

Dog—Tick—Tick—Man.

Bandicoot—Tick—Tick—Man or by direct infection or through milk.

Weyer (1954) has made important observations on the behaviour of various species of rickettsia in the body louse (pediculus), *Rickettsia quintana*, *R. prowazeki*, *R. mooseri*, *R. conori* (Kenya tick-typhus and South African tick-bite fevers), *R. rickettsii*, *R. akari*, *R. tsutsugamushi* and *Coxiella burnetii*. All these, except *R. tsutsugamushi* and *R. quintana* multiply or survive in the hæmolymp of larvæ of the meal worm (*Tenebrio molitor*) and in the tick (*Ornithodoros moubata*). Without exception they multiply in the hæmolymp of the louse and can be passaged through the lice by intracoelomic inoculation, though after a certain number of passages *T. tsutsugamushi* ceases to multiply in the coelom. All, except the latter, can multiply in the stomach of the louse.

When inoculated into the rectum all, except *R. tsutsugamushi* and *R. rickettsii*, can be passaged repeatedly from louse to louse by rectal inoculation. *R. conori* may be pathogenic and cause severe damage to the mucosa of the stomach and death within 3-7 days.

Morphology.—In their morphology in human tissues (Wolbach and Todd) rickettsiae appear as small bacilli or cocci, very variable in arrangement. Diploid forms and also coccoid forms in dense masses are common (Fig. 45). With the possible exception of *R. tsutsugamushi* they stain well by Giemsa's method, and blue with Castañeda's stain (Fig. 46); with Macchiavello's stain they are red and the containing cell blue. None of the species

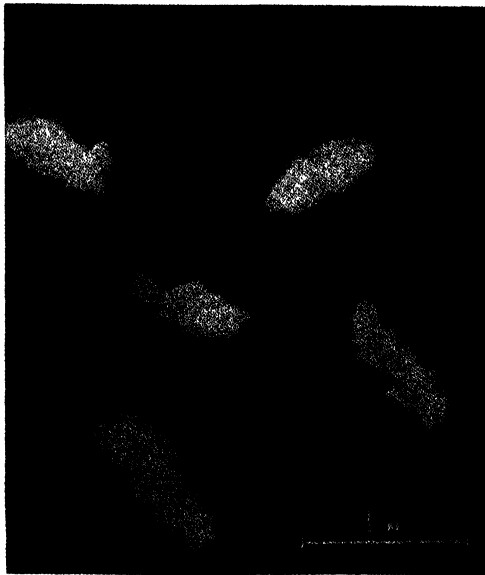


Fig. 45.—Electron micrograph of chromium-shadowed *R. prowazeki*.
(Weisseemann et al., 1951.)

can readily be cultivated on solid media. Practically pure strains of *R. prowazeki* are obtained by intrarectal injection of lice with infected material, as practised by Weigl, but attempts to culture them from human tissues have so far been unsuccessful. All rickettsiae grow readily on the chorio-allantoic membrane, or preferably in the yolk sac, of the developing chick embryo, whilst Gispén (1941) has shown that ducks' eggs are highly suitable. The rickettsiae do not cause death of the embryo, though they produce big, round, prominent foci five days after inoculation and develop completely in 7-8 days. They grow in tissue cultures and in a medium of minced chicken embryo with a mixture of guinea-pig or rabbit serum and Tyrode solution.

In all laboratories in which work is done with typhus rickettsiae workers are liable to attack, in spite of previous inoculation, so that vaccine

cannot completely protect against infection by the respiratory route that occurs in these cases, though it greatly reduces the severity of the attack. The infection may also be spread by dust contaminated by louse

Although there is evidence that rickettsiæ will grow in the presence of non-living cells, yet they require their presence and thus resemble viruses rather than bacteria which can be grown on artificial media. With the exception of *R. (Coxiella) burneti*, pathogenic rickettsiæ are difficult to filter through Seitz or porcelain filters. Rickettsiæ can be grouped provisionally between the true viruses and bacteria.



Fig. 46.—*Rickettsia prowazeki*, var. *mooseri*. ("Mooser cell.")

Tunica vaginalis of guinea-pig infected with murine typhus from wild rats. Cytoplasmic rickettsiæ invading a mononuclear cell. Giemsa stain. Approx. $\times 4,000$ (Anigstein and Bader. Galveston, Texas).

Pinkerton has pointed out that the two main forms of typhus—the louse-borne and the tick-borne—may be differentiated by the cellular reaction they produce.

Typhus, conveyed by lice and fleas, usually during the winter months, is characterized by invasion of the endothelium and mesothelium by rickettsiæ, producing distension of the cytoplasm of the host cells without affecting the nuclei, while in guinea-pigs it causes proliferative endangiitis without thrombonecrosis. In typhus-infected lice and fleas rickettsiæ are intracytoplasmic, inhabiting the lining cells of the gut; they are not hereditarily transmitted.

The *spotted fever group*, conveyed by ticks, is characterized by thrombo-necrosis of arterioles and venules. The rickettsiæ in human tissues invade smooth muscle cells, endothelium, mesothelium and histiocytes. In *tissue-cultures* a massive infection of the nuclei takes place. In infected ticks the organisms are *intranuclear* as well as intracytoplasmic, invading nearly all types of tissue and they are hereditarily transmitted. These are suggestive distinctions.

Differential reactions.—The *Neill-Mooser reaction* is a distinctive reaction in guinea-pigs inoculated with typhus blood. A redness and swelling of the scrotum appears and typical typhus lesions are found in the scrotum in the endothelial lining of the tunica vaginalis; swollen cells packed with rickettsiæ are seen in sections. Some strains, notably *R. rickettsii*, give this reaction more strongly than others; it is also present in about 70 per cent. of epidemic typhus in early guinea-pig passage and nearly always in the murine type. Raynal and Fournier have pointed out that a somewhat similar orchitic reaction may be caused by *Salmonella paratyphi B.*, and also by *Spirillum minus*, but the reaction produced occurs later, lasts longer and the scrotum is harder.

AGGLUTINATION REACTIONS AS A MEANS OF DIFFERENTIATION

The only serological test formerly available was the Weil-Felix reaction, using strains of proteus known as *OX2*, *OX19* and *OXK*. While louse- and flea-borne typhus gave positive agglutination with *OX2* and *OX19*, mite-borne typhus reacted with the *OXK* (*K* for Kingsbury) strain. The Weil-Felix reaction was by no means specific, for cases of undulant fever, relapsing, and rat-bite fever give a positive agglutination reaction, more especially with *OXK*. Suspensions of *Proteus OXK* are liable, especially in the tropics, to become unsuitable for performing agglutination tests. It should be remembered that, in those inoculated against typhoid or paratyphoid fever, the onset of typhus may cause a rise in the agglutination titres against *Salmonella typhi* and *S. paratyphosum* A. and B. Diagnosis is now made by agglutination of rickettsial suspensions and by complement fixation, using rickettsiæ from the infected yolk sac of the developing chick embryo as antigen.

A complement-fixation test using a rickettsial antigen has also been devised.

Treatment.—All rickettsial diseases of man are amenable to anti-biotic treatment and in this group they are specific.

In this table *boutonneuse* fever and African tick-bite fever are classified together. American tick-borne fever is Rocky Mountain spotted fever.

Dosage schedules. Loading dose.—This is 50–60 mgm./kgm. body weight followed by the same daily doses given in three or four divided doses till defervescence. Average duration of fever in mite-borne (scrub) typhus after treatment is 81 hours for chloramphenicol, 25 hours for chlortetracycline, 87 hours for oxytetracycline. Similar results are obtained in Brill's disease and in rickettsialpox. No death occurred in 588 cases of rickettsial disease. *Side effects* are vomiting and diarrhoea.

THE TYPHUS GROUP OF FEVERS

AVERAGE DURATION, IN DAYS, OF FEVER AFTER FIRST DOSE OF ANTIBIOTIC

(From Ley and Smadel, 1954)

(A) TYPHUS GROUP OF FEVERS					(B) Q. FEVER
LOUSE-BORNE	FLEA-BORNE	MITT-BORNE	TICK-BORNE		
			AMERICAN	AFRICAN	
Chloramphenicol (Chloromycetin)	2	3	2	4	3
Chlortetracycline (Aureomycin)	3	2	2	3	5
Oxytetracycline (Terramycin)	4	3	2	4	3

occasionally. N.B.: Fatal attacks of aplastic anaemia may follow prolonged treatment with chloramphenicol. "Recurrence of infection" may follow about one week after end of short course of antibiotics in *scrub typhus* when given too early in course of infection which suppresses antigen and antibody formation before immunity has been established.

I. EPIDEMIC OR LOUSE-BORNE TYPHUS

Synonym.—True exanthematic, historic, or classical typhus; Tabardillo (Mexico). Chronic form: Brill's disease.

Definition.—An acute fever, louse-borne, abrupt in onset lasting about fourteen days and, if not fatal, terminating by crisis about that time. The pyrexia is remittent. On or about the fifth day there appears a roseolar eruption tending to petechiae spreading from the abdomen over the trunk and extremities. As was stressed by Zinsser and MacArthur, this form of typhus must be considered the most important disease in history.

Geographical distribution and epidemiology.—Typhus is world-wide. Still common in E. Poland, N.W. Soviet Russia and Ukraine. (Between 1917–1928, 30,000,000 cases with 8,000,000 deaths in European Russia.) India, N.W. Frontier, N. Africa, N. Nigeria, Belgian Congo, E. and S. Africa, Cochin China, Central and S. China, Korea, Manchuria, Sumatra, Philippines, N.E. Australia, Japan, Mexico, and Abyssinia. Formerly frequent in England and Ireland. (In 1942 a limited epidemic occurred in Galway, Eire (Stuart-Harris and others) (Map IV).)

In 1932 there was a big outbreak in Uganda, especially in districts of over 5,000 feet altitude. Similar occurrences have been reported in the Himalayas and Afghanistan.

Typhus can thus occur in tropical countries as well as in those with a cold climate.

There was a new wave in 1933 in Egypt and Chile, in 1934 in South Africa, in the Soviet Union, Rumania, Poland, Yugoslavia, Portugal and

Hawaii. Typhus is most frequent in winter and spring months when heavy clothing affords an opportunity for lice-breeding.

Ætiology.—*Rickettsia prowazeki*, the specific organism, is conveyed by the louse (*Pediculus humanus*, var. *corporis* and *capitis*); in the blood during the first five days it is filterable and infective for monkeys and guinea-pigs as the rickettsiæ are present in the blood-plasma, especially in the blood-platelets. A development cycle of the rickettsia takes place in the intestinal tract of the louse (see p. 218). Infection is conveyed by the louse faeces, which are inoculated into scarified skin by scratching. Löffler and Mooser (1942) showed that head-lice play an important part in transmission. *R. prowazeki* was first seen in epidemic typhus in 1910 by Wilder.

Typhus blood was found infective for guinea-pigs and monkeys by Ricketts, Nicolle and Anderson; later Wolbach, Todd, Palfrey and Pinkerton (1920-22) found intracellular *R. prowazeki* in lice in Poland. Nicolle, Comte and Conseil proved by experiment that the chimpanzee can be infected by lice.

So many physicians died of typhus during the 1914-1918 war, and so many contracted the disease, that other methods of transmission than by lice were suggested and it is probable (as accepted in the second world war) that the rickettsiæ may also be conveyed as a droplet infection. There are German reports that infection has been acquired by medical attendants while taking blood for the Weil-Felix reaction. Typhus has also been conveyed by blood transfusion when the donor happened to be in the incubation period of the disease.

Pathology.—The rash is usually visible after death. There are conjunctival hæmorrhages and, as a rule, areas of skin necrosis and gangrene. The blood is particularly dark and does not clot. The kidneys and liver show cloudy swelling. The spleen is usually moderately enlarged, with hyperplasia of the lymph follicles; the substance is soft and diffuent. Bronchial catarrh is usually present, with hypostatic pulmonary congestion.

The eruption is due to proliferation of the endothelium and localized necrosis of the walls of the smaller blood vessels, with local collections of lymphocytes and plasma cells in the adventitia. These are the "typhus nodules" which resemble miliary tubercles, first described by Fränkel and subsequently by Aschoff, Wolbach and others. They are characteristic, and are found in the vessels of the skin, myocardium, brain and viscera (Fig. 47). The essential lesion is due to phagocytosis by cells of the vascular endothelium, followed by necrosis of those which enclose rickettsiæ and their toxins. Lesions in the brain, resembling miliary tubercles, are found especially in the basal ganglia, medulla and cerebral cortex.

The red marrow becomes hyperplastic and is converted into yellow marrow, though there is little increase in the myeloid elements. The circulatory failure of typhus is regarded by some observers as being a peripheral vascular failure and is attributable to damage to the capillaries or to injury of the vasomotor centres, or to both these factors, but the myocarditis cannot be ignored. The disease is a vasculitis commencing

with damage to the endothelial cells of the capillaries which are invaded by rickettsiæ and there is evidence that a true rickettsial pneumonia can result, and the organisms can be seen in sections of the lung. The occurrence of vasculitis, hyaline threads, nodulæ and diffuse accumulations of



Fig. 47.—Typhus nodule. Section of arteriole of skin showing attached mural thrombus, composed almost wholly of phagocytic endothelial cells, with early proliferative perivascular reaction.

(After Wolbach and Todd.)

mononuclear cells, myocarditis, myositis and nodules in the central nervous system are diagnostic of rickettsial infections.

Symptoms.—It has been said that the more clinicians see of typhus the more varied becomes the clinical picture. The disease varies within wide limits. A particularly mild or larval form was originally described by Brill in 1898 amongst the Jewish population of New York (Brill's¹ disease).

¹ Sometimes also known as Brill-Zinsser disease.

The infection was brought in by immigrants from the typhus regions of S.E. Europe, so that 90 per cent. of cases occurred in foreign-born people. Its incidence is sporadic and it is now regarded as the inter-epidemic form of epidemic, louse-borne typhus. Thus Rupe (1958), reports a late relapse of louse-typhus eight years after the first attack and a similar one in a man born in Turkey who had lived in the U.S.A. since 1916. In neither case was there any evidence of recent exposure. The best designation is probably "recrudescent epidemic typhus."

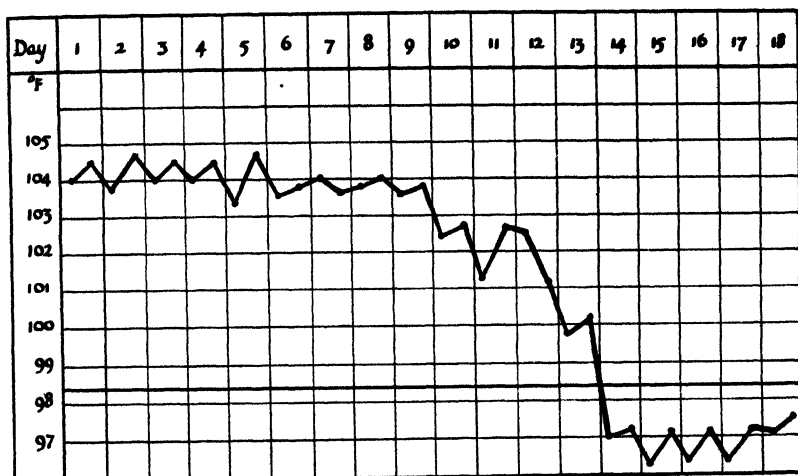


Chart 12.—Typhus Fever.

The *incubation period* varies between five and twenty-three days, the average being twelve. The period of onset lasts about two days, during which the patient has rigors, headaches, pains in back and limbs, nausea and giddiness. Vomiting is frequent. Occasionally, fulminant cases (*typhus siderans*), with general convulsions and delirium, are met. On the third day the temperature rises suddenly to 103° or 104° F., the face becomes congested, with general suffusion of the eyes. The headache is very severe (German—*Kopfwehkrankheit*) and with it goes a peculiar stuporose, drunken look not seen in any other disease except perhaps, plague. The patient is drowsy, often delirious (coma-vigil), usually with insomnia.

The mouth is foul, the tongue coated with a dense brown fur, the breath offensive. Epistaxis is frequent in the early stages and vomiting may be distressing. For twelve to fourteen days the temperature remains raised with slight, sometimes scarcely perceptible, morning remissions (Chart 12). The urine is concentrated, offensive, with a cloud of albumin, urea and chlorides initially increased in amount. In severe cases there is often hæmaturia. The spleen is usually enlarged and palpable. German observers lay great stress on the changes in the cardio-vascular system, especially the low systolic and diastolic blood pressures.

The *rash*, so characteristic of typhus, may appear as early as the third day, but more usually on the fifth or sixth, upon the abdomen, inner aspect of the arms, spreading over the chest, back and trunk, usually pleomorphic, involving the face only in severe cases. It may be absent in about 10 per cent. The term "mulberry rash" is usually employed to describe it, but it essentially consists of roseolar macules, with fine, irregular dusky mottling underlying the epidermis, best described in the words of Murchison as "*subcuticular mottling*." Usually it becomes

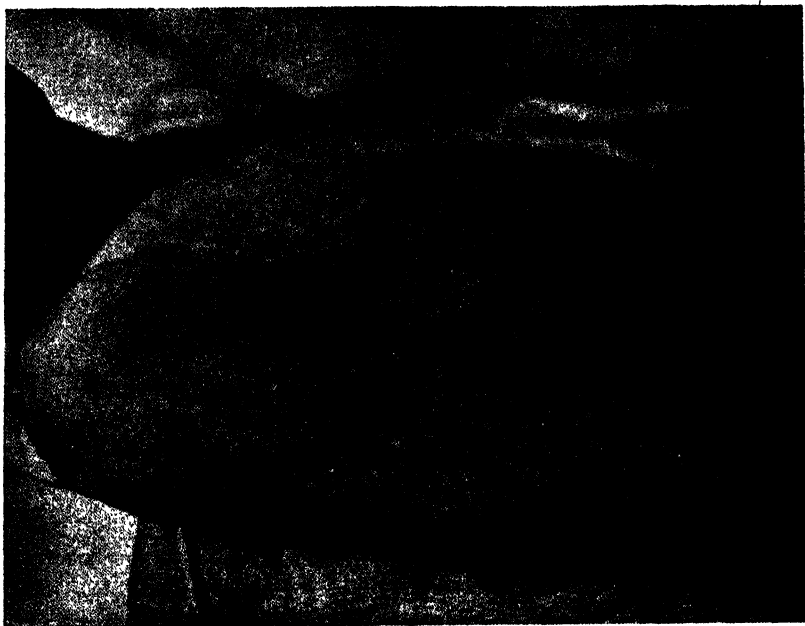


Fig. 48.—Typhus rash in second week, showing typical distribution. The dark coloured areas are petechial; the lighter coloured, less discrete areas disappear on pressure. (After Wolbach and Todd.)

petechial and may then be seen especially on the hands and soles of the feet (Fig. 48).

Rarely, it is bright red, instead of a mingling of copper and purple; sometimes, too, it may be hæmorrhagic. Papular spots are commonly encountered and may be circular or indefinite, but when petechial they may closely resemble flea bites. The rash fades very slowly and may remain visible for ten days. A fine brawny desquamation towards the end of the third week has been described; it sometimes occurs on the soles of the feet.

In dark-skinned natives the typhus rash is necessarily very difficult to discern. To make the subcuticular mottling visible, a thorough cleansing of the skin and a good light are necessary. Congestion of

the upper arms by a tourniquet, such as the band of a blood-pressure apparatus, usually renders the petechiæ more easily visible. This method has also been practised with success in the early diagnosis of the typhus rash in Europeans. In natives the rash is usually more pronounced around the umbilicus.

On the appearance of the rash there are usually signs of bronchitis and in severe cases sometimes icterus; prostration and cardiac weakness become more pronounced, and with increase of the mental lethargy the patient sinks into the "typhus state." The expression becomes dull and vacant, the face flushed, with a peculiar earthy hue (*facies typhosa*). Cerebration is slow; the hands and tongue are tremulous and the patient becomes more difficult to nurse. The skin at this stage sometimes emits an odour which has been compared to that of "gun-washings," or that emanating from a cupboard containing well-blackened or mouldy boots.

During the second week a low muttering delirium usually supervenes. Meningism is not uncommon. The secretion of urine may then be diminished or even suppressed. Often symptoms of cortical irritation, such as muscular twitchings, and incontinence of urine and fæces may be observed. The cerebro-spinal fluid is under pressure and there is usually an increase in the cell content. It is estimated that 80 per cent. suffer from all degrees of deafness. Especially common are septic infections of the middle ear which usually appear from the sixth to eighth day (Mittermaier).

In severe cases the pupils become pinpoint and the eyes "ferrety." As the fourteenth day approaches, signs of improvement may set in; the temperature falls by crisis, or sometimes by rapid lysis. Death generally occurs on the twelfth or fourteenth day, or it may be later, when the temperature is subnormal, from exhaustion or cardiac failure. The blood picture usually shows nothing very definite, but a moderate leucocytosis of 12,000 to 15,000 per c.mm., mostly of large mononuclear cells, is not unusual. The blood is concentrated so that the hæmoglobin and red blood count are abnormally high.

Amongst indigenous populations terrible complications due to sepsis and neglect may ensue. Terminal bronchopneumonia is common. The patients become extremely emaciated. Involvement of the central nervous system is frequent, such as ataxia, violent tremors, mania or dementia. Hemiplegia or paresis of the limbs due to typhus nodules in the brain has been reported. Parotitis and noma are frequent. Abortion in pregnant women is common. Constipation rather than diarrhœa is the rule. The mouth becomes very foul, with the lips and teeth covered with sordes. Bedsores are frequent. Thrombosis of the femoral vein is not uncommon, while gangrene of the extremities, especially of the toes or scrotum, due to arterial thrombosis, is frequently seen in wartime epidemics. One of the most distressing features is gangrene of the lung as a termination of typhus bronchopneumonia. Mental symptoms are among the most important sequelæ. Recently it has been suggested that juvenile thrombo-angiitis obliterans (Bürger's disease) may be due to antecedent typhus.

Relapsing fever and typhus frequently co-exist and this superadded infection is serious. Mild forms of typhus, lasting some ten days, are

frequently seen in children, but it is usually the very young, the aged and the ill-fed who most readily succumb. Aberrant forms of typhus fever without a rash may be encountered towards the end of an outbreak when immunity is high.

Convalescence is usually slow and prolonged, and during this period great care should be taken not to excite the heart. Snapper pointed out that thrombocytopenia is not infrequent in typhus and some cases, even after the typhus infection is over, show a typical anaphylactoid, sometimes even a thrombocytopenic purpura. Loss of hair on the head and legs is said to be common.

The case mortality is negligible in children. It is 10–15 per cent. up to the age of forty, but 50 per cent. at fifty; over that age few survive. Relapses of typhus have been recorded. It appears that epidemic typhus has become so solidly established in man that some individuals, who have recovered from a first attack, retain the rickettsiæ in their bodies and may develop a second many years after the first, at such time as when the bodily resistance is depressed.

Immunity.—On recovery from an attack of typhus the immunity is complete for a considerable time, but this gradually wears off. Apparent or mild attacks in persons with partial immunity are believed to constitute an important source of infection.

Diagnosis.—Conditions which may simulate typhus are readily differentiated by laboratory methods. As has already been noted, the rashes of other members of the typhus group closely simulate that of exanthematic typhus and can be distinguished with difficulty. Stress is laid on the rarity of rash on the face and the fact that it does not come out in crops. The “tongue sign”, first described by Okuniewski, is said to be very helpful in bed-side diagnosis. The patient is unable to protrude the tongue when ordered to do so; this is attributed to perivascular infiltration in the region of the nucleus of the hypoglossal nerve. The smell is characteristic of mouldy leather.

The *Weil-Felix* reaction in high dilution is diagnostic, but false positive reactions may occur in infective hepatitis, enteric, relapsing and undulant fevers. The titre of agglutination rapidly rises to 1 in 500 towards the end of the fever. During convalescence it remains about 1 in 50–1 in 100 for weeks and even months. A reliable strain of *Proteus* OX19, as from the Oxford Standards Laboratory, should be employed.

Felix states that the type of titre curve is generally related to the clinical course: (a) moderately severe cases usually show high-titre reactions, (b) most-severe cases usually give very low titres, and (c) the mildest cases have either very low or very high titres. In countries where typhus is endemic, the titre of normal persons may be above 1 : 100. Subsequent to antityphus inoculation with rickettsiæ of the OX19 group (*R. prowazeki* and *R. mooseri*) agglutinins often appear, but titres are usually low. For carrying out the test, round-bottomed test-tubes, 2 by $\frac{1}{2}$ in., are employed. Lower dilutions such as 1 : 25 and 1 : 50 should always be included. The tubes are incubated for two hours and are read after 22 hours at room temperature or, in the tropics, after the same time in the ice-chest. Readings with a lens at the end of two hours often assist

in the early detection of high-titre reaction. This is often delayed and the maximum titre is usually reached in the third or fourth week.

The Weil-Felix test is no longer regarded as absolutely specific and most workers now use agglutination or complement-fixation tests with suspensions of rickettsiæ.

A pseudo-positive Wassermann reaction is frequently given by the blood before the crisis. Fever is seen in male guinea-pigs in from six to ten days after intraperitoneal inoculation.

A complement-fixation reaction (Bengtson and Topping) appears to be reliable and may become a routine procedure when specific antigens become more generally available. Bengtson summarizes the results: of 216 sera giving a positive fixation for Rocky Mountain fever 92.1 per cent. had no cross fixation for endemic typhus antigen. Amongst 114 sera positive for endemic typhus 80 per cent. gave no cross fixation for Rocky Mountain fever. The long persistence of the complement-fixation reaction is a valuable feature as it facilitates retrospective diagnosis. (This statement applies to all members of the group.)

The rickettsiæ may be isolated from the blood at the height of the fever by inoculating 2-5 ml. intraperitoneally into male guinea-pigs and subsequently demonstrating rickettsiæ in the tunica vaginalis. Gear and Davis showed that South African gerbilles (*Tatera brantsi* and *T. afra*) are specially susceptible to typhus and die with heavy infection of the peritoneum. Exposure of these animals to X-rays definitely lowers their resistance.

Skin biopsy for the identification of the rash has been proved particularly useful. Sections show the typical lesions resembling periarteritis nodosa. The petechiæ in the skin are due to thrombosis of the smaller vessels.

An intradermal test was introduced by Giroud (1938). The patient's serum is mixed with a definite quantity of rickettsiæ (emulsion of the tunica of a guinea-pig infected with the murine strain). The emulsion is injected into the skin on the inner surface of the thigh of a rabbit. Normal serum is used as a control. If the patient has, or has had typhus, no reaction appears, but in the controls it is marked.

Fleck (1947) has described the presence of a substance in the urine with the characters of a specific antigen of typhus rickettsiæ. It may appear in the first days and in an amount sufficient to give a precipitation reaction, and when injected into rabbits it gives rise to rickettsial and OX19 agglutinins.

Differential diagnosis.—This has chiefly to be made from typhoid and is based upon the onset and course of the temperature curve and in the character of skin eruption. In typhus the temperature climbs quickly to a high level where it remains, in place of the slower escalator rise of typhoid fever. There is, moreover, a mild leucopenia in typhoid: a mild leucocytosis in typhus. The diffuse roseolar rash of paratyphoid (especially paratyphoid A) may sometimes resemble that of typhus, but nervous signs and symptoms are less severe, and roseola of palms of hands and soles of feet is not found in typhoid as in typhus.

The differential diagnosis from *septic meningitis* with skin eruptions

may be difficult, and determinable only by examination of the cerebro-spinal fluid and by the Weil-Felix reaction. Differential diagnosis has also to be made from measles, especially the malignant form, commonly observed in native races. In this case Koplik's spots are of assistance; moreover, in measles the rash is brighter, its edges are definitely more marked and it is more profuse on the face. In the tropics, dengue, especially in the initial stages, may prove difficult, but the patient is never so ill, nor is suffusion of the face so marked. In severe smallpox the initial scarlatiniform rash may be confusing, but characteristic smallpox lesions are seen first on the face. Cerebro-spinal fever, purpura and relapsing fever have to be considered; the latter is frequently found in combination with typhus.

Treatment.—Special attention must be paid to details of nursing and to the hygiene of the mouth. The recumbent position is essential, and every precaution should be taken against bedsores. It is important that the patient should have as much fresh air as possible. It is customary to give stimulants, the most favoured being port wine—about eight ounces in twenty-four hours being sufficient.

Cardiac stimulants are indicated, such as tincture of digitalis, digitalin (gr. $\frac{1}{10}$) or digitoxin (digitaline crystallisée gr. 1/100). Strychnine gr. $\frac{1}{80}$ is also a good stimulant. Lumbar puncture should be employed to relieve delirium and other cerebral symptoms, for, as a rule, the cerebro-spinal fluid is under pressure. Plenty of fluids should be given and the diet should be as nutritious and easily digestible as possible.

Antibiotics (see p. 218).

Chloromycetin (*Chloramphenicol*) 0·1 grm. per ml. is dissolved in propylene glycol, stored in rubber-capped vials containing 10 ml. for parenteral injection. The dosage is 1·5 grm. daily for 2–3 days. Tablets for oral medication each contain 0·25 grm. chloromycetin. The results following slow intravenous injections are rapid. Within three hours headache and backache showed improvement and vision becomes normal.

Streptomycin is of curative value. Smadel has shown that it inhibits rickettsiæ of typhus and Rocky Mountain fever, but not those of mite typhus. Nitroacridine and *p*-amino-benzoic acid possess a synergistic action when given together with streptomycin.

Aureomycin was given by Sanchez in Mexico to forty-two patients in divided doses by the mouth. The daily dose was 50–75 mgm. per kg. and treatment for 36 hours usually sufficed. Nausea and vomiting, when present, need not necessitate interruption of the treatment.

Prophylaxis.—The quarantine period of typhus is fifteen days. The main prophylactic measures consist almost exclusively in the destruction of lice. The body should be shaved, including the pubes and axillæ, the hair of the head cropped and a cresol bath taken.

A great advance has been made by the use of DDT, which is the active ingredient of louse powder. (For further details, see p. 854).

Prophylactic inoculation.—Several methods of active immunization against louse-borne typhus are in use in various parts of the world.

II. MURINE TYPHUS—FLEA TYPHUS

Synonym. Endemic typhus (shop typhus in Malaya).

Geographical distribution and epidemiology.—This is worldwide, especially in Mexico, North America, India and Palestine. Typhus-infected rats have been found in the Mediterranean basin, Syria, Greece, Toulon, Malaya, North and West Africa and the Belgian Congo. The seasonal incidence remains constant; the majority of cases occur in summer and autumn. The incidence is twice as high in males as in females and the negro is less susceptible than the European. In West Africa this form has been found not uncommonly where it had not previously been suspected, both in ports and in inland districts. The urban, or shop, typhus of Malaya (Lewthwaite) and India (Rice), which in both places is local in distribution, is also murine typhus. Murine typhus caused 5,388 cases in the Southern United States in 1944. (Map IV).

Ætiology.—Nicolle in Tunis and Zinsser in America took the view that murine typhus is the more primitive disease. It is clear that it is not spread from man to man, but from rat to man, the brown rat, *Rattus norvegicus*, being mainly concerned in temperate climates. They think that the infection may overflow to man, generally producing isolated cases without further man-to-man spread. According to an evolutionary point of view, this infection has undergone two mutations, by changing both its vertebrate and invertebrate host. In Mexico a type of typhus exists in rodents and man which may be regarded as intermediate between the murine and louse-borne types. It is also true that many species of rickettsia are unstable. The more recent origin of epidemic typhus is indicated by the fact that *R. prowazeki* var. *mooseri* is harmless to the flea, while *R. prowazeki* causes death of the louse, to which it may be regarded as less adapted. It therefore appears probable that the endemic form may be easily converted into the epidemic, and that typhus infection may be maintained in the inter-epidemic period by rats. Thus, Raynal, Fournier and Velliot (1939) have adduced evidence in Shanghai that, under certain conditions, the rat rickettsia can be converted from the rat-flea-rat cycle into the man-louse-man cycle. The armadillo and the field rat in S. America are susceptible to murine typhus (Varela and Mazzotti).

Weyer has shown that the mouse flea, *Leptopsylla segnis*, is susceptible to *R. mooseri*. Intracellular strains of rickettsia, virulent for mice, sometimes become extracellular and non-virulent after transfer through the flea and further passage through lice.

On epidemiological grounds the association of endemic typhus with rats and grain stores was first suggested by Hone (1922) in Australia and subsequently by Maxcy (1926) in America; in 1931 proof was provided by Mooser, Dyer and his colleagues that the rat was the reservoir, and that rat fleas (*Xenopsylla cheopis* and *X. astia*) were carriers. Under normal conditions the infection is spread from rat to rat by the rat-louse (*Polyplox spinulosa*). Rats (*R. norvegicus*)

collected from areas where numerous cases of endemic typhus had occurred, were chloroformed, then the fleas collected, emulsified and injected intraperitoneally into guinea-pigs. After four days' incubation period these reacted with fever and swelling of the testes (Neill-Mooser reaction).

Rickettsia of Murine Typhus in Mites.—Trombiculid mites, *Schöngastia indica*, have been found naturally infected with murine typhus. The mites were taken from house rats (*R. rattus diardi*) and sewer rats (*R. norvegicus*). Emulsions of the mites were given intraperitoneally to mice which died in ten days. In guinea-pigs the strain had the microscopical characteristics of *R. mooseri* (Gispen, 1950).

General considerations.—Other forms of typhus resembling murine typhus have been described from Australia, North and South Africa, whilst ship-fever of Toulon (*fièvre nautique*) is a local form; other varieties may be those forms of trench fever with a rash, and also the urban (W) form of tropical typhus described by Fletcher and his colleagues in Malaya with a tendency to spread amongst those engaged in handling grain.

Symptoms.—The symptoms resemble those of epidemic typhus, but are much milder in every respect. The mortality rate is very small (about 1·5 per cent).

Treatment.—(See p. 218).

Prophylaxis.—Reports from U.S.A. indicate that the incidence of murine typhus has been much reduced by applying 10 per cent. DDT to rat runs, burrows, and harbourages.

III. MITE TYPHUS—SCRUB TYPHUS (see Map IV.)

Synonyms.—Tsutsugamushi; Tropical typhus; Shimamushi; Japanese river fever; Kedani mite disease; "K form."

Definition.—A typhus disease with a high case-mortality rate, characterized by the presence on the skin of an *initial eschar*, supervening on the bite of a species of microtrombidium (the larval stage of *Trombicula akamushi*—a "velvet mite"). This is followed by an ulcer, lymphangitis, and a typhus-like rash. Audy has shown that it is in reality a zoonosis.

Geographical distribution.—In Japan the disease is limited to areas near the banks of rivers on the west side of the main island and endemic in the Niigata province from May to October. In Formosa and in the main island it is widely distributed, not only near river banks, but in cultivated fields, foothills and mountains (up to 6,500 ft.). The peak period is July to October. In the Pescadores Islands the houses are surrounded by the endemic area and all the inhabitants are exposed to infection. The disease is not contracted in the fields. The peak period is April to November. In Borneo fatal cases have been reported in Brunei. In New Guinea the disease is widespread, in New Britain, and Papua. In Queensland it is known as Mosman, scrub or coastal fever and occurs in the eastern coastal area between Cooktown and Ingham. In Java cases are reported from Bandoeng; in Sumatra, in workers on tobacco estates in the north. In Malaya it is known to occur in Selangor,

Pahang, Perak, Kedah and Negri-Sembilan. In Indo-China it occurs in five divisions—Cambodia, Cochin-China, Annam, Laos and Tonking; in Burma—in Lower Burma, Rangoon, Syriam, Henzada, Prome, Toungoo, Bassein; also in Upper Burma and Thailand (Siam). It also occurs in S. China, Hong Kong, Java; in India, probably in the Simla Hills, Madras and Bombay. In Ceylon a few cases have been reported from the south-east part of the island.

Epidemiology.—The patchiness in distribution of trombiculid mites has been much commented upon. Mites seem to be limited to certain areas, particularly to tracts that were once under cultivation and are relapsing again into jungle. So accurately can this "typhus country" be defined that risk of infection can be foreseen fairly accurately from aerial photographs. Another striking feature is the wide variation, not only in infection rate, but also in mortality. There is no evidence of any difference in the virulence of local strains of *R. tsutsugamushi*, but considerable variation in the number of rickettsiæ that can be recovered from local trombiculids (*Trombicula deliensis*). The areas of greatest infectivity are on the mainland of New Guinea where mite-rat-mite passage is most easily effected. This was seen in South Bat Island (Lat. 2° 50' S., long. 146° 14' E.), in the Purdy Group, which is uninhabited except by pigs, flying foxes and a saturated population of rats infested with mites (*T. deliensis*) and *R. tsutsugamushi*. Thereon 26, of a total of 41, sailors and soldiers in 1944 contracted scrub typhus within 46 days and 2 died. In Upper Burma the peak of the disease roughly corresponds with the beginning and end of the monsoon, when *T. deliensis* is most abundant, but it may be acquired in any month of the year. The main factors are exposure to mite infestation together with fluctuation of the mite population. An infected site remains hazardous for at least one year. Transovarian transmission of *R. tsutsugamushi* has been demonstrated to explain this feature. The mite is regarded as the vector of the infection and rats as transitory reservoirs. In this area the Yunnan buff-breasted rat (*Rattus flavipectus yunnanensis*) and the Assamese tree-shrew (*Tupaia belangeri versurae*) are found naturally infected with *R. tsutsugamushi* (Mackie). In New Guinea and adjoining islands the types of infected localities are (1) open kunaigrass land, (2) abandoned banana and coconut gardens, (3) sparse, coarse growth of native vegetation, (4) areas on the edge of virgin forests.

The risk of contracting scrub typhus is great in the fringe of forest clearings in Malaya where the mite vectors are most common. Thus rubber plantations, overgrown by weeds, cleared jungle and abandoned vegetable gardens, are dangerous. In these localities rickettsiæ are found in pools of *T. deliensis* and *T. akamushi* collected from the jungle rats—*Rattus rattus argentiventer* (Audy) (see p. 1025).

It is necessary to note that these larval mites do not digest blood, but only lymph and tissue fluids and they do not remain attached to their animal hosts for more than 3–4 days.

Outside the endemic area it has been shown by Noury that the Moroccan rodent—*Meriones shawi*—is susceptible to intraperitoneal inoculation with *R. tsutsugamushi*.

What is known as "winter scrub typhus" in Japan is probably spread by the mite known as *Trombicula scutellaris*. The fever is recognized locally as "Schichito Fever." *T. scutellaris* has a much wider distribution in Japan than *T. akamushi* (Sandosham, Suzuki, 1956).

Ætiology.—The organism of "scrub typhus" is known as *Rickettsia tsutsugamushi* (*orientalis*). This organism is conveyed by the bite of an acarous (locally known as *akamushi*—the red insect), which is the larva of "velvet mites," either *Trombicula akamushi* (0·9 mm. in length) or *T. deliensis*. The adult stage is non-parasitic. This larva is popularly known as the kedani mite or "patau" (Figs. 369–371, p. 1027). The Japanese have always regarded it as the vector of this fever. (This mite somewhat resembles the harvest mite—the larva of *T. autumnalis*—and was formerly and incorrectly known as *Microtrombidium* or *Leptotrombicula akamushi*.) In Sumatra and Malaya, however, the vectors are larvae of *Trombicula deliensis* and *T. schiffneri* respectively, which infest the undergrowth and long grass ("lalang") in clearings of the forest and there they are probably distributed by the crow pheasant (*Centropus bengalensis javanicus*). *T. deliensis* is pale ochre in colour: *T. akamushi* bright vermilion. The larval trombicula occurs numerously on the ears of the field vole (*Microtus montebelloi*) and other rodents—*Mus jerdoni*, *R. rattus refuscens*, *R. decumanus* and *R. agrarius*. In Korea and Formosa it is disseminated by a small warbler (*Acrocephalus stentorius orientalis*), domestic fowls, the pheasant (*Phasianus colchicus formosanus*) and a quail (*Turnix javanica atrigularis*). In the Mandated Territory of New Guinea, Gunther (1939) has always regarded *T. minor* as the probable vector, its principal hosts being the rat or bandicoot (*Echymipera cockerelli*), bush pig, fowl, turkey, cassuary and ground pigeon. In Papua the vector is probably *T. hirsti* or *T. fletcheri* (65·7 per cent. of mites on rats and bandicoots in New Guinea were found to be *T. fletcheri* from which *R. tsutsugamushi* was recovered).

As has been shown by Audy the association of micro-trombiculæ with rats forms a natural assemblage known as a *Biocenose* and is a "parasitic pattern." The jungle rats are the normal host of microtrombiculæ and also act as the reservoir host of *Rickettsia tsutsugamushi*. There is formed a recurrent cycle between the rats and the mites; man is only accidental and is a spill-over from the cycle. The cycle in the infected areas is kept up by jungle rats *Rattus r. jalorensis*, *R. r. concolor*, and *R. r. argentiventer*, which in turn transmit to the Malayan house-rat *R. r. diardi* in towns, as in Kuala Lumpur.

The rickettsiæ have been found in the body-cavity of the adult mite, *Trombicula akamushi*, and in the salivary glands of the infective larval stage, but are now known to persist from one generation to the next—about 30 days.

R. tsutsugamushi occurs in the blood in the incubation period of the disease. Monkeys can be easily infected with as small a quantity as 0·001 ml. The organisms are destroyed by heating at 55° C. for ten minutes.

Nagayo and others succeeded in transmitting the rickettsiæ by intra-ocular inoculation in guinea-pigs, also by intratesticular injection in

rabbits, in which they produce a characteristic reaction. Cross immunity experiments have shown that no immunity exists between *R. tsutsugamushi* and *R. prowazeki* and that therefore these two members of the typhus group are distinct.

Pathology.—The lesion at the site of the infective mite bite undergoes coagulation necrosis and affects the epidermis, corium and surrounding tissues and is well delineated by a boundary line. This forms the *eschar*, or ulcer, which is usually, though not invariably, present. The spleen is enlarged, with tense capsule, soft, friable pulp, and focal necrosis; similar lesions are found in the enlarged and congested liver. The kidneys show pale swelling of cortex and a narrow zone of congestion. The lungs are congested; hypostatic bronchopneumonia is frequent, with pleural effusions. There is a general lymphadenitis; glands in the vicinity of the initial lesion are specially affected and may show central necrotic lesions. There is usually an effusion of clear fluid in the tunica vaginalis. There is generalized cedema of varying degree and hæmorrhages into the body tissues.

Kouwenaar found that histologically the "typhus nodules" differ from those of the louse-borne form in that the chief change is the perivascular infiltration and that the intima of the blood vessels is secondarily involved.

Symptoms.—The person attacked by the mite does not usually notice the bite, but later feels a pricking sensation when he happens to touch the spot. Generally it crawls up and bites at first obstruction at bend of elbows. The mite, or mites, can easily be seen through a strong magnifying glass, with their heads and bodies buried in the skin, but only when they are carriers of the disease do any definite pathological changes take place round the lesions they inflict. After an incubation period of from four to ten days or longer, the disease begins with severe frontal and temporal headache, anorexia, chills alternating with flushes of heat. Presently the patient becomes conscious of pain and tenderness in the lymphatic glands of the groin, armpit, or neck. On inspection of the skin of the corresponding lymphatic area there is sometimes discovered—usually about the genitals or armpits—a small (2–4 mm.), round, dark, tough, firmly adherent eschar with necrotic centre surrounded by a painless livid red areola of superficial congestion. This is the initial ulcer (Fig. 49). Sometimes it may be merely a papule, which develops and disappears during the incubation period and therefore is seldom visible. Lewthwaite makes a point that an *ulcer* is not by any means invariable. Occasionally two or three such eschars are discovered. Although a line of tenderness may be traced from the sore to the swollen, hard, and sensitive glands, no well-defined cord of lymphangitis can be made out. The superficial lymphatic glands of the rest of the body, especially those on the side opposite to the glands primarily affected, are also, but more slightly, enlarged.

Clinical observers in Burma describe adenopathy as present in 90 per cent. The glands are most noticeably palpable in the posterior triangles of the neck. In a few cases this is so pronounced as to give a bull-neck

appearance. The enlargement of the posterior occipital glands may be the cause of occipital pain in association with neck rigidity.

Fever of a continued type now sets in, the thermometer mounting in the course of five or six days to 104° or 105° F, reaching its maximum at the 48 hours. The conjunctivæ become injected; the eyes are half-closed, watery and faintly glistening. Photophobia is invariable. At the same time, a considerable bronchitis gives rise to harassing cough. The pulse is full and strong, ranging rather low—80 to 100—for the degree of fever



Fig. 49.—Mile Typhus. *Eschar with enlarged satellite lymph node.
(Dr. T. J. Danaraj, Singapore.)

present. The spleen is moderately but distinctly enlarged, and there is marked constipation.

About the sixth or seventh day the eruption of large dark-red papules appears. It is usually maculopapular, sometimes papular or macular. It lasts 3–4 days, mainly on the trunk, upper arms and thighs. It sometimes extends to the face, hands and feet.

During the height of the fever the patient is flushed and at night may be delirious. He complains incessantly, probably on account of a general hyperæsthesia of skin and muscles. Deafness is also a constant feature.

As the disease advances, the symptoms become more urgent; the

conjunctivitis is intensified, the cough becomes incessant, the tongue dries, the lips crack and bleed, and there may be from time to time profuse perspiration. By the end of the second week—sooner or later according to the severity of the case—the fever begins to remit by lysis, the tongue to clean and, after a few days, temperature falls to normal and the patient speedily convalesces. There is a well-marked leucopenia. When the leucocytes are increased some extraneous infection may be suspected. The red cells are normal, but there is a decrease in the coagulability of the blood. Bronchitis, diarrhoea, or diuresis may occur during the decline of the fever. The circular, sharp-edged, deep ulcer left after the separation of the primary eschar—usually during the second week—now begins to heal, and the enlargement of the glands gradually to subside. The urine is albuminous and gives the diazo-reaction.

Such is the course of a moderately severe case. In some instances, however, the constitutional disturbance is very slight, although the primary eschar may be well marked and perhaps extensive. On the other hand, the fever may be much more violent, and complications, such as parotitis, melæna, coma, mania, cardiac failure, or œdema of the lungs may end in death. Similarly, the duration of the disease varies according to severity from one to four weeks, three weeks being about the average. Relapses do not occur.

Dame (1946) found eye sequelæ in 98 per cent., especially subjective retinal findings consisting of enlargement of blind spots, contraction of visual fields, and scotomata. Minor non-specific involvement of the cochlear system of the ear was found in only 11 per cent. during convalescence.

Pregnant women contracting scrub typhus mostly abort and die.

According to Hatori, reinfection may occur.

The death-rate in Japan is high—from 25–80 per cent.—but much lower in Sumatra (0–15 per cent.). In Burma and New Guinea the mortality in British and American troops was from 10–15 per cent. In peace times the mortality varies from 0·6–35 per cent. (Philip).

Diagnosis.—The Weil-Felix reaction has proved of great value in diagnosis (*see p. 217*). The serum does not agglutinate suspensions of OX19, or OX2, but only OXK (Kingsbury strain) and this appears to be quite clear and definite. The main type of antigen is therefore OXK. Filtrates of OXK have been employed for an intradermal test (Kuroda). A positive reaction is said to supervene within a period of two hours, during the first few days of the illness only, but a negative reaction ensues after the sixth or seventh day.

United States medical authorities report that *R. tsutsugamushi* is readily isolated in the early stages by grinding up blood clot with normal saline and centrifuging at low speed; 0·8 ml. of the supernatant fluid is inoculated intraperitoneally into mice. Death occurs 10–16 days later, when rickettsiæ are demonstrated in peritoneal smears. Blake, Maxcy and colleagues have found the Syrian hamster most suitable for passage of rickettsiæ after intraperitoneal inoculation. Wedd (1945) regards the speckling of the lymphocytes with azurophilic granules as diagnostic; the maximum counts are obtained during convalescence. The detection

of antigen in the urine can be made as early as the first day of the illness by the hæmagglutination-inhibition test of O'Connor and McDonald (1952). They used red blood corpuscles sensitized by the polysaccharide antigen of *Proteus* OXK which acts as an inhibitor of hæmagglutination by the antibodies of mite-borne typhus, in the same manner as Milovanovic and Stojkavic have found the corresponding antigen of *Proteus* OX19 inhibits hæmagglutination by antibodies of louse-borne typhus.

The limited geographical distribution, together with the initial necrotic ulcer and lymphadenitis, suggest the diagnosis. Plague and tularæmia may possibly be considered, but even if primary vesicles or ulcers occur in these diseases, the matting together and exquisite tenderness of the lymphatic glands should be suggestive.

The differentiation of measles and dengue may also have to be decided.

Treatment.—On account of the helplessness of these patients and their inability to feed themselves expert nursing is vital. Nasal feeding is necessary in very severe cases (Willcox). The site of the bite should be treated by cauterization or extirpation. Common salt, 6–8 grm., should be given freely.

Chloromycetin (chloramphenicol) (*see* p. 217).—The action of this drug was first investigated in Malaya by Smadel, Lewthwaite and Savor. Twenty-five patients were treated (1948) with twelve as controls.

Among those treated none died and no complications developed. The duration of the fever after the first dose averaged 31 hours and the whole febrile period 7·5 days. At first, the same large doses were given as in louse-borne typhus, but gradually dosage was reduced till only 6 grm. was administered in 24 hours to the last seven patients, and the results were equally good. Prezyna and others (1954) in treatment of this disease in the Pescadores consider that the three main antibiotics (*see* p. 218) are equally effective. In the case of aureomycin and oxytetracycline (terramycin) the initial dose is 3 grm., followed by a second dose of 2 grm. after 12 hours.

Prophylaxis.—Dibutylphthalate is lethal to mites, which are killed when walking on impregnated cloth. Two ounces of *dibutyl phthalate* (DBP) suffices to treat two sets of tropical uniform (blouse, trousers, underclothes, socks, etc.). Each man is issued with the fluid, which he smears on to his garments. The fingers are dipped into the fluid, the hands are then rubbed lightly together over the cloth, which is thus smeared with DBP. Experience indicates how many smears are needed to cover each garment efficiently, i.e., six smears per sock, thirty for trousers, etc. DBP resists up to eight washes in cold water, wading through rivers, heavy rain, etc. As a repellent, 5 per cent. emulsion of DBP in 2 per cent. soap emulsion is effective. Snyder and Morton advocated a mixture of equal parts of benzyl benzoate and dibutylphthalate as most effective and more persistent than benzyl benzoate alone. Other prophylactic measures in endemic areas consist of cutting or burning the long kunai grass, or "lalang", as it is known in Malaya and subsequently spraying with oil. The local rats which act as vectors of the mites must be destroyed as much as possible and prevented from entering dwellings. (For prophylactic inoculation, *see* p. 248.)

The spraying of dangerous areas with crude oil and the smearing of the legs of estate labourers with the same oil and the use of BHC (gammexane) dust at the rate of 1 lb. per acre are advocated. More recent insecticides, such as aldrin and dieldrin show great efficacy in controlling the trombiculid mite vectors in Malaya (*see* p. 861).

Chemoprophylaxis.—Smadel has advocated the use of chloromycetin as a prophylactic by giving 1.0 grm. daily by the mouth to volunteers. The drug was given during the days of exposure to risk and for 13 subsequent days. Between the twelfth and twenty-sixth days, after first exposure. 71 per cent. of untreated controls were attacked by scrub typhus. It was shown that in the treated group the disease was suppressed till at least eight days after the cessation of treatment.

The only significant difference between the attacks in these two groups was that no eschars occurred amongst the treated.

IV. TICK TYPHUS—ROCKY MOUNTAIN SPOTTED FEVER

Synonyms. Rocky Mountain Fever; Black Fever; Blue Disease.

Definition.—A specific fever supervening on the bite of ticks—*Dermacentor andersoni* and *D. variabilis*—and resembling, symptomatically, louse-borne typhus. Other species of tick have also been incriminated.

Geographical distribution and epidemiology.—First described in 1896, it was originally thought to be confined to several of the Western States of the American Union: Idaho, Montana (Bitterroot Valley), Wyoming, Utah, Nevada, Oregon, Colorado, New Mexico and Washington States. It is now known to be divisible into two varieties, eastern and western. On the whole, the latter is thought to be the more deadly. The eastern form is gradually spreading and has been reported from 32 States, as well as from E. British Columbia, Alberta and Saskatchewan, the only U.S. States not infected being Maine, New Hampshire, Vermont, Connecticut, Wisconsin, Rhode Island, Michigan and Kansas (Map IV, p. 218).

Principally found in valleys and near the foothills of the mountains, it occurs in sharply-defined and limited areas. A new South American focus in Colombia was originally discovered by Patiño-Camargo (1935) on the Tobia river, a tributary of the Rio Negro, in a narrow valley of the Magdalena basin at an altitude from 2,800 to 4,100 feet, and a second, somewhat to the north-west, on the Villeta at 1,650–4,800 feet. The high death rate (95 per cent.) and the susceptibility of laboratory animals to inoculation made it probable that the rickettsia is identical with *R. rickettsii*. The tick vectors appear to be *Amblyomma cajennense* and *Dermacentor nitens*.

In the north-western regions of the United States the vector is *Dermacentor andersoni*, which is prevalent from the middle of March to the middle of June, and in that region the majority of cases occur in April, May and June, occasionally in July and September. In eastern States the vector is *D. variabilis* which appears in March and December; most of the cases are reported in June, July and August. The infection conveyed by these ticks is therefore more common in women and children because dogs bring ticks into the houses. Gould and Mieose (1954) have

succeeded in isolating *R. rickettsii* from one out of 65 meadow mice (*Microtus pennsylvanicus*) collected in Virginia where patients suffering from this fever were believed to have contracted the infection.

It has become apparent that spotted fever is more widely distributed in America than was formerly considered probable, and that two principal types of the group in the Western Hemisphere can be distinguished—one transmitted by ticks of the genus *Dermacentor*, the other by *Amblyomma*; the latter covers the greater portion of Texas and a large part of South America.

Ætiology.—The organism is now known as *Rickettsia rickettsii*. There is conclusive evidence that *R. rickettsii* is introduced by the bite of wood tick; only the adult normally attacks man (see p. 1082).

The natural hosts of the wood-tick, *D. andersoni*, are the Rocky Mountain goat, sheep, black bear, coyote, badger and lynx, but the larval stages develop principally on ground squirrels (*Citellus columbianus*) and the woodchuck (*Marmota flaviventris*). According to Bishopp and Smith, the immature stages of the dog tick (*D. variabilis*), are found on the meadow mouse (*Microtus pennsylvanicus*). The disease tends to occur in the spring months when these ticks abound. These facts naturally gave rise to the idea that the animals acted as reservoirs of the disease.

The larva, nymph, adult male and female ticks have been proved efficient intermediaries for the parasite, whilst Dyer and others showed that the rickettsiæ are transmitted through the egg to the larva in a hereditary manner.

The proportion of infected ticks under natural conditions is quite small—only 1 in 296 in Ricketts' experience. He originally suggested from differences in the case mortality (in Montana 90 per cent. : in Idaho 5 per cent.) that two species of tick were capable of transmitting infection—*D. andersoni* and *D. variabilis*—and the suggestion proved correct. After feeding on infected blood there is a period of invasion which lasts 12 days, during which a multiplication of rickettsiæ takes place and they are converted into what is known as "tick virus."

The work of Parker and colleagues, in Oklahoma, and of Anigstein and Bader in Texas (1948) afford grounds for believing that spotted fever intergrades between the South American form on the one hand and *fièvre boutonneuse* on the other. In an outbreak in Oklahoma the typhus infection was transmitted by nymphs of *Amblyomma americanum* and in infected guinea-pigs the rickettsiæ were identical with *R. rickettsii*. The natural reservoir in this case was for the first time proved to be a rodent, the pocket gopher (*Geomys breviceps dutcheri*). In Texas, evidence pointed to the dog as the natural reservoir, to the dog tick (*Rhipicephalus sanguineus*) as the vector, as well as *A. americanum* and probably also *A. maculatum*.

In human tissues Wolbach first observed minute bodies (*R. rickettsii*) staining with Giemsa, within the endothelium of blood vessels, in the substance of human and guinea-pig testes. The same forms were identified in the bodies, salivary glands and eggs of *Dermacentor*.

Pathology.—In addition to the skin rash, there is usually bronchopneumonic consolidation, or hypostatic congestion of the lungs, with subserous petechial hæmorrhages. Similar lesions are frequently seen in

the brain. The myocardium is softened; the spleen enlarged and firm; the lymphatic glands generally enlarged; focal necrosis of the hepatic cells and congestion of the renal cortex are found. Constant lesions, both in man and in artificially infected animals, are hæmorrhages into the genitalia and, quite often, gangrene of the prepuce and scrotum. Vascular nodules are a constant feature, but not so striking as in typhus, with perivascular mononuclear infiltration. Rickettsiæ are found in endothelial cells and in smooth muscle cells of the vessel walls.

Symptoms.—The incubation period is 3–7 days. The attack is ushered in by chills which are repeated with diminishing severity at irregular intervals throughout the attack. By the second day the temperature rises to 108° or 104° F. and by the fifth to 105° or 107° F. A typhus condition supervenes, with intense headache, photophobia, irritability and meningeal irritation. If the patient is to recover, the temperature begins to fall at the end of the second week and the fever usually subsides by lysis. There are intense muscular pains and very often an agonizing arthritis.



Fig. 50.—Rocky Mountain spotted fever on tenth day, showing confluent hæmorrhagic areas and a necrotic pressure area of the skin over the buttock. Texas outbreak conveyed by *Amblyomma americanum*. (By courtesy of Dr. L. Anigstein.)

The rash appears from the fourth to seventh day. It is first seen as small rose-coloured spots resembling measles, but soon becomes petechial, spreading so as to become confluent, especially on the more dependent parts, though it may occasionally be seen on the forehead. It is, on the whole, redder and more florid than that of louse-borne typhus. Later it spreads to palms, soles of feet and scalp. In some cases the spots remain discrete, brownish or purplish, giving a speckled appearance. Slight icteric tinging of the skin and conjunctivæ is frequently observed. In some cases gangrenous patches of skin occur on the elbows, toes and lobes of the ears. During the third week desquamation sets in and the eruption gradually fades. (Fig. 50.)

Constipation is the rule. The liver is usually enlarged; the spleen enlarged, firm and tender. Albuminuria is due to kidney involvement,

and the highly-coloured, concentrated urine usually contains casts. Severe cases are characterized by œdema of the face and limbs. Nausea and vomiting set in about the beginning of the second week and in fatal cases may persist throughout. Respiration is rapid, owing to respiratory catarrh. The pulse loses in volume as it increases in frequency. The erythrocyte count is little affected; the hæmoglobin content is slightly reduced and there is a mild leucocytosis of 12,000 to 18,000 per c.mm. There is a reduction in the blood-platelet count. Complications, such as gangrene of the tonsils, scrotum and prepuce, are common in the milder form. A high degree of immunity is produced and no instance is known of a second attack.

It is now recognized that there is little evidence for the view that eastern and western types can be distinguished.

Diagnosis.—The sudden onset, the intense muscular and joint pains, together with a negative Widal reaction, help to differentiate it from typhoid. The geographical distribution remains a most important factor in its separation from louse-borne typhus. The serological reactions belong to the indeterminate group. A feeble agglutination with *Proteus* OX19 occurs and also with OX₂ and OXK. Guinea-pigs are easily infected and develop the Neill-Mooser reaction with swelling of the testes and scrotum. (For complement-fixation and agglutination of rickettsiæ which are more specific than the Weil-Felix, see p. 217.)

A differential table is given by Cumming and Millam between Rocky Mountain fever and endemic typhus (flea-typhus).

Rocky Mountain Fever.

Rural.

History of tick bite.

Children.

Several cases in the same family.

Fever up to 107° F., lasts for weeks and ends by lysis.

Rash on wrists, then general, including palms of hands and soles of feet.

Mortality 25 per cent. or over.

Endemic Typhus

Urban.

Premises infested with rats and fleas.

Adults and middle-aged.

Sporadic.

Fever lower, ends by crisis in second week.

Rash first on trunk, flexor surface of limbs, rarely on face, palms or soles.

Mortality under 5 per cent.

Mortality varies considerably. In Montana it has been as high as 75–90 per cent. The percentage given by Topping (1941) was 19·4 for the western and 18·1 for the eastern form.

Treatment.—*Chloromycetin* (chloramphenicol) is as satisfactory in the fever as in other forms of typhus (see p. 218).

Prophylaxis.—Attempts at prophylaxis have been carried out on the basis of the known methods of transmission. War is being waged on ground squirrels and woodchucks, the natural hosts of *D. andersoni*. Domestic stock, especially sheep and goats, are being systemically dipped with arsenicals, to prevent the spread of the tick. It must be borne in mind that *D. andersoni* does not infest human dwellings.

On the whole, the sheep is an uncongenial host; badly infected districts should be converted into sheep-runs. Workers in endemic areas



1a



2



- 1.—Rash of trypanosomiasis (*T. gambiense*). (Dr. F. Murgatroyd).
- 1(a).—Primary lesion, site of infecting tsetse bite on leg.
- 2.—Dengue rash (after Cleland, Bradley and MacDonald).
- 3.—Rash of febre boutonneuse on legs (after D. and J. Olmer, 1933).

IVII

RASHES

should be clad in a one-piece costume, the trousers should be tucked inside woollen socks and the sleeves secured with a strap at the wrists. Tick bites should be immediately cauterized or, if possible, excised. *D. variabilis* is frequently brought into houses by house dogs, which may be freed from infection by the application of powdered derris root. Gammexane appears to be more lethal to ticks than DDT and can be used also as a repellent (*see* p. 861).

V. TICK TYPHUS (FIÈVRE BOUTONNEUSE) TICK-BITE FEVER

Synonyms. Marseilles fever; eruptive fever; *fièvre exanthématique*; *escharo nodulaire*; tick-bite fevers—South African, South American and Indian forms.

History and geographical distribution.—*Fièvre boutonneuse* (caused by *Rickettsia conori*) was first described by Conor and Bruch in 1910 in Tunis, but is now known to occur throughout the Mediterranean littoral; also in Marseilles and many other districts in Southern France, as well as in Italy, Portugal, Spain (Jaurez), Greece, Roumania and the Crimea. This fever is transmitted by *Rhipicephalus sanguineus* in the Crimea and in other parts of S. Russia by *Dermacentor nuttalli*, *D. silvarum* and *Hæmaphysalis concinna*. It has been found by Jadin and Panier (1958) that a rickettsia of the Boutonneuse type is prevalent in Ruandi-Urundi in the Belgian Congo and is conveyed by *Ornithodoros moubata*.

Distinctive features.—The distinctive features of this fever are that the rickettsia is transmitted by the common dog-tick, *Rhipicephalus sanguineus* (Durand, Conseil, Brumpt, 1930) and that the dog constitutes the reservoir of the virus, for these animals have been shown to be susceptible and their blood infective both for man and monkeys (Durand). The tick-transmitted virus (*Rickettsia prowazeki* var. *conori*) can pass hereditarily from one generation of tick to another without necessarily passing through a reservoir animal. It has been pointed out that, though intra-nuclear rickettsiæ have been seen in the human tissues, they are much less numerous than in the North American spotted fevers. Hereditary transmission through the tick *Hæmaphysalis leachi* has been proved.

Another distinctive feature is the appearance of a primary sore, often in the axilla, at the site of the infecting tick-bite which, becoming gangrenous, is known as "*tache noire*", and varies in size from a pin's head to a pea, but is not usually painful. Lymphangitis subsequently occurs. These features are comparable with those of tick-bite fever of South Africa (Troup and Pijper, 1931) and of mite typhus. Gangrene of the scrotum has been described in an African by de Gac and Giroud.

VI. OTHER FORMS OF TICK TYPHUS

African Tick Typhus.—The tick-bite fever of South Africa, West Africa, East Africa, the Sudan, Eritrea, Somaliland, Mombasa and Ethiopia, originally described by McNaught in 1911, and again by Pijper and Dau in 1934, resembles *fièvre boutonneuse*, but is conveyed by

larval ticks—*Amblyomma hebraeum*, *Rhipicephalus appendiculatus* and *Boophilus decoloratus*. In the Cape Province the local dog-tick *Hæmaphysalis leachi* is the vector (Gear and Douthwaite). In South Africa tick-bite fever has a varied epidemiology. It is contracted more often in the fields or on the veld than in urban areas. Sporadic cases have been reported from Johannesburg, Kenya and Ethiopia at the height of 5,000 ft. These small ticks climb on to grass, attaching themselves to man and animals and, being veld dwellers, are not found in houses or on domestic animals. The disease in this respect resembles Rocky Mountain fever. In nature, infection is conveyed by tick-bite, and rickettsiæ can be demonstrated in the Malpighian tubules of the ticks; an emulsion produces the disease in animals and a slight Neill-Mooser reaction in guinea-pigs. The serum reactions in man are not quite clearly cut. In most cases *Proteus* OXK is agglutinated in a higher titre than OX19. Pijper and Crocker (1938) have shown that the rickettsia of this tick typhus does not immunize against the louse-borne or murine forms.

Heisch (1957) has shown that in Kenya, at any rate, tick typhus behaves as a zoonosis. Rickettsiæ have been isolated from *Hæmaphysalis leachi*, *Rhipicephalus simus* and *Amblyomma variegatum*, all of which occur on dogs. An African volunteer inoculated with a strain of *Rickettsia* from *R. simus* developed typical tick typhus and rickettsiæ were recovered from his blood. Later reports by Heisch, McPhee and Rickman (1957) show that brain emulsions of the rodent *Otomys angoniensis* and spleen extracts of *Lemniscomys* produce rickettsiæ when injected into guinea-pigs. These Kenya strains of rickettsiæ when tested by Gear by complement-fixation seem to be closely related to, if not identical with, those of South African tick-bite fever *R. conori* var. *pijperi*. Heisch has also described a "Backgarden" zoonosis in Nairobi residents who develop tick typhus when bitten by the dog-tick *Rhipicephalus simus*.

Two forms of African "tick-bite fever" are described: mild, or abortive, and fully developed. In the first the only symptom may be the primary sore, accompanied by adenitis and lymphangitis at the site of the bite. In the fully-developed form, in addition to the primary manifestations, the fever lasts ten days, with severe headache, stiffness of neck, conjunctivitis and petechial rash on the fifth day. It is apt to be confused with cerebro-spinal meningitis, measles and typhoid fever.

Gear and Douthwaite regard the dog as the reservoir of infection in South Africa, especially in the Cape Province, where it is suggested that the local dog-tick *Hæmaphysalis leachi* may transmit the infection.

South American Tick Typhus.—South American tick typhus, also sometimes known as "Tabardillo," or "burning fever," is a form of tick typhus common in Minas Geraes, Brazil (Magalhaes, 1940); it resembles *fièvre boutonneuse* and may be the analogue of Rocky Mountain fever farther north, as Parker, Davis and Dyer have shown that there is cross-immunity. It is possibly the same as the rural disease which has occurred in Colombia and Texas (see p. 236) and Montiero succeeded in transmitting the rickettsiæ through the tick *Amblyomma cajennense*, producing intraocular lesions in guinea-pigs and monkeys by the injection of infected human blood.

Rickettsiæ were demonstrated in the endothelial cells of Descemet's membrane.

The mortality is said to be high—about 80 per cent. Ambulatory forms are recognized. There is usually a local lesion and adenitis. The grave forms are associated with sudden onset, severe pains, vomiting and delirium. Magalhaes found a leucocytosis up to 59,800 per c.mm. in 74 per cent. of the cases; leucopenia is exceptional; in severe attacks the blood urea is as high as 205 mgm. per cent. The urine is scanty, urea content diminished and there is chloride retention in the majority of cases. The Weil-Felix reaction is not clear-cut (Fialho, 1932); agglutination with OX19, OX2 and OXK is found in low dilutions. Dias (1938) stated that the natural reservoirs are the opossum, domestic and wild dog (*Cercopithecus*), the wild rabbit (*Sylvilagus brasiliensis*) and the agouti (*Dasyprocta*). The tick vectors are several species of *Amblyomma*:—*A. cajennense*, *A. striatum*, *A. brasiliense*; the former especially, according to Dias, is commonly parasitic on the domestic dogs.

Indian Tick Typhus.—McKechnie (1911) found a mild sporadic form of typhus in the Kumaon Hills on the North-West Frontier districts of India, and Megaw (1916) suffered from such an attack which he attributed to the bite of a tick. Other cases have been reported by Stott (1935) from Lucknow and by Webster (1939) from the Simla hills, but there is also evidence that mite-borne typhus exists in parts of India.

North Queensland Tick Typhus.—A mild form of rickettsial disease has been described in North and to a lesser extent, in South Queensland. It produces a syndrome resembling "boutonneuse." Although it is antigenetically related to this group, it is differentiated by a specific complement-fixation reaction. The rickettsia has been provisionally named *R. australis*. The vector is probably *Ixodes holocyclus*. Complement fixation antibodies have been found in four species of small marsupials—bandicoots, kangaroo rats, and bush-tailed opossums. There is an eschar with regional adenopathy, a rash and typhus-like clinical course.

Siberian Tick Typhus.—A tick-borne rickettsial disease has been reported from east and central Siberia. It is a mild form with primary eschar, adenitis, headache and rash. The vectors are ticks—*Dermacentor nuttalli*, *D. sylvarum* and *Hæmaphysalis concinna*. Transovarian transmission has been demonstrated in these species.

VII. " Q FEVER " (QUERY¹ FEVER)

History.—A new fever was noted in 1935 in meat-workers in Brisbane, Queensland, by Burnet and Freeman, and since then many cases have been described. By 1939 it had been realized by Dyer and his collaborators that the organism—*Rickettsia burneti*—is the same as that described in America as *R. diaporica*, which is spread by the ticks, *Dermacentor andersoni* and *Ornithodoros turicata*, in Wyoming and the Western United States. This organism has recently been renamed *Coxiella burneti*, Parker, a terminology which has been accepted. In recent years this

¹Not Queensland Fever as has been erroneously stated.

fever has become increasingly common in almost every country and a great many and varied sources of infection have been described. It is a very common and easily contracted "laboratory infection" and quite recently an outbreak has been reported from a Cambridge University laboratory from a blocked drain (Stoker, 1957).

Geographical Distribution and Epidemiology.—At first considered a medical curiosity confined to meat workers in Queensland, it soon became realized by the experiences in the Second World War that Q fever is wide-spread and that many outbreaks of atypical pneumonia in the Mediterranean theatre were due to this infection.

In 1947 four familial outbreaks were observed in Switzerland. In the next year Caminopetros showed that goats and sheep in Greece were infected with *C. burneti* and in the same year outbreaks were reported in sheep, goats, cattle and buffaloes in Turkey and its existence established in Israel and in Germany. Q fever was then found to be widespread in America with large outbreaks in Montana, Texas, California and Panama. There is evidence, too, that the disease is present in Morocco and to the south in Casablanca and Agadir, also in Corsica, France, Iraq, Tunisia, South Africa, Congo and Kenya. Blanco (1955) has isolated *C. burneti* from wild-caught *Hyalomma* in Spain and has demonstrated it in 44 per cent. of rabbits. Most outbreaks in European countries are spread by droplet infection. Numerous laboratory infections from handling cultures have been described (Oliphant and Parkes, Nauck, Weyer, and Stoker in Cambridge, 1957). No evidence has been forthcoming of its existence in New Zealand.

Rickettsiae of *C. burneti* are excreted in the milk of infected animals, in the placenta and in the amniotic fluid. Sheep are susceptible via the respiratory tract, especially when climatic conditions favour rapid drying and dissemination of infective material. Ticks also take part, but cannot be infected continuously from one generation to another so that their efficiency as vectors is poor in comparison to the mite of scrub typhus. For instance, Stoker and Marmion have shown that, at least, one species of tick collected from sheep in Romney Marsh is infected with *C. burneti*. The basic cycle of wild animals and ticks clearly exists and may be more extensive than appears at present, but is probably of secondary importance. *C. burneti* can exist, it seems, under the most adverse conditions, for outside its host it can resist drying and pasteurization is barely able to destroy it. Inside its host it can persist for long periods and can do this even in the presence of antibody.

The presence of Q fever has been confirmed by serological tests in many countries and the few exceptions are those where the import of cattle and sheep is restricted. Where ticks and other arthropods are concerned the picture is rather different and there are only a few isolated cases. In Queensland and in South Australia in abattoirs it is spread by *Ixodes holocyclus*. One outbreak in the Belgian Congo with 40 deaths, and the isolation of *C. burneti* from their body lice, is recorded by Jadin and Giroud.

Pazzin has described an outbreak in a Turkish village in which inhalation of dust from infected wool was held responsible and Klopstock a similar occurrence in Israel. Gsell had a somewhat comparable experience

in Switzerland in men engaged in unpacking heavy goods from America. An outbreak in Chicago slaughter houses was ascribed to handling freshly-killed meat and in California Q fever is common in those attending cattle. while *C. burneti* has been found in fresh milk in Texas. Irons and colleagues have found that 5 per cent. of slaughter men harbour complement-fixation antibodies for Q fever. In England, Stoker (1949) found serological evidence in meat handlers and isolated *C. burneti* from milk during the



Fig. 51. *Coxiella burneti* (*diaporica*). American Q Fever.
(Wyoming, U.S.A.)

(Slide prepared from peritoneal scrapings of infected guinea-pig by
L. A. Nigstein, Galveston, Texas.) Giemsa. $\times 1500$.

outbreak in the Royal Cancer Hospital in London. A larger outbreak was found in Canterbury School by Harvey and others in 1951 and a third in South Kent by Stoker and Thompson in 1953. Furthermore, examination of the milk from 108 herds in Kent showed that 8.2 per cent. were excreting *C. burneti* and that the highest incidence is in the south east. In addition to Queensland already mentioned there are many reports of tick transmission in southern Europe, North Africa and in the U.S.A. De Prada isolated the organism from the blood of man, as well as from

the tick *Hyalomma savignyi*, in Salamanca, Spain; Sussman from *Rhipicephalus sanguineus* collected from a dog in Phoenix, Arizona; Jellison from an argasid tick—*Otobius megnini*—in California; Blanc and Bruneau from *Hyalomma mauritanicum* in Algeria, and from the merion (a gerbille) and its tick *H. excavatum lusitanicum* in Morocco; Winn and Lennette from *Haemaphysalis punctata* in Southern Rhodesia as well as from the wool of infected sheep; from *Hyalomma dromedarii* and from Sudanese bulls in Egypt (Taylor and Mount, 1953). Blanc and Bruneau (1955) have proved the maintenance of *C. burneti* under natural conditions in the rabbit (*Oryctolagus cuniculus*) in North Africa, as well as in the tick, *Ornithodoros erraticus*. Besides its ability to exist in ticks, and lice, Weyer and Nauck have established that *C. burneti* can be maintained in meal worms, but superabundance of growth kills them off in one week. It is now known that the "Congolese Red Fever," originally described by Clapier in 1921 is merely an exanthemic form of Q fever as it occurs in the Congo.

Etiology.—*Coxiella* (*R.*) *burneti* is morphologically similar to *C. (R.) diaporica* (Fig. 51) and produces characteristic pathological effects in monkeys, mice and guinea-pigs. There is a well-defined febrile reaction, during which time the blood is infective for guinea-pigs. Mice inoculated intraperitoneally show enlargement of liver and spleen with characteristic histological changes. In sections and smears of infected mouse liver and spleen large numbers of rickettsiae occur in relatively large intracytoplasmic colonies (Fig. 51). It is the smallest of all the rickettsiae and is filterable. In experimental animals it has to be distinguished from Goennert's virus disease of mouse lung. Fluorescent microscopy is of special value in estimating the number of rickettsiae in yolk-sac cultures (Urbach and Sprössig, 1958).

This method is not recommended for the investigation of the structural details.

C. burneti can be cultivated on minced chicken embryo reaching its maximum growth during the second week. When eight or nine-day embryos are inoculated, in membranes removed after six days and incubated at 34° C, numerous rickettsiae are visible. After numerous passages on egg-membrane the American strain shows no reduction in virulence for guinea-pigs. Cox and Bell similarly cultivated the American strain in chicken embryo, in flasks containing yolk sac tissue suspensions and filtered human ascitic fluid, in which it develops more profusely than does the Australian coxiella.

The natural reservoir in Queensland is the bandicoot (*Isodon torosus* or *obesulus*), which is very susceptible to experimental infection.¹ Smith and Derrick (1940) isolated the rickettsia from a tick, *Haemaphysalis humerosa*, which is normally an ecto-parasite of the bandicoot and opossum. Derrick and Smith found that cattle may play an important part in transmission, and that human disease may result from direct infection from the body tissues of infected cattle, or further indirect infection from them by the body tissues of ticks, especially *Boophilus annulatus microphis*.

Since 1938 it has been ascertained by Davis, Cox, Dyer and others that the

¹ This animal is a marsupial and is quite distinct from the bandicoot rat (*Neoskia bandicota*).

organism, *R. diaporica*, which was first isolated from the tick, *Ornithodoros turicata*, is identical with *R. burneti* and should be known as *C. burneti* var. *americana*. Davis (1940) showed that it may persist in the tissues of this tick for three years. The range of susceptible hosts is the same in both varieties but the American (Montana) strain appears to be more virulent except for mice. *Dermacentor occidentalis* and *Amblyomma americanum* also harbour the rickettsiae. There is some evidence that transovarian transmission may take place in the tick.

In Morocco *C. burneti* has been isolated from the spleen of infected merions (*Meriones shawi*) as well as from ticks, *Hyalomma savignyi* and *H. excavatum*, var. *lusitanicum* found living in the burrows of this North African rodent.

Burnet and Freeman confirmed the findings of Dyer that the *C. burneti* of Australia and of America are identical. Both Montana and Australian Q strains are agglutinated to the same titre by sera from a number of animals experimentally infected with one or other strain. Sera from man and animals infected with other rickettsial diseases do not agglutinate *C. burneti*. Guinea-pigs protected against Rocky Mountain fever are not immune to Q fever, but protection against Q fever is active against the virus recovered from wood ticks (*D. andersoni*) in Montana and the serum of patients recovered from Q fever protects against both Australian and American strains. As with other rickettsial infections, mixtures of virus and immune serum in suitable proportions may be injected into animals without febrile response, but in all instances the subsequent complete immunity of the animal indicates that actual infection has indeed taken place.

C. burneti is present in the blood of man during the fever period only, but may be found in the urine during the later stages. It is also present in the pulmonary cases in the sputum and can be conveyed to mice and guinea-pigs by this means.

Pathology.—The pathology has been described by Whittick (1950). The lung resembles lobar pneumonia. Coccoid and bacilliform rickettsiae can be clearly demonstrated in the mononuclear cells and degenerated macrophages when stained with Giemsa; also in the testes and in the neuroglia cells of the brain.

Symptoms.—This fever is known in America as "Nine-mile fever." The onset in man is acute and sudden. The course and duration vary considerably. It is very infectious. In Europe and America it is probably commonly conveyed by dust, not by droplet contamination. Milk from cattle and goats may be a vehicle. Sometimes there is a rapid deferescence after six to nine days; sometimes the course is protracted to the third, or even to the fourth week and the temperature falls by lysis. There is no rash as in other forms of rickettsiasis. The outstanding symptom is headache which may be extremely severe and persistent, while the pulse-rate is slow. The disease is comparatively mild and there have been no fatalities.

Hornibrook and Nelson reported an outbreak in 15 persons amongst 158 employed in one building in North America. No valid evidence was obtained in this instance that any arthropod was concerned with the outbreak, or in the transmission of the disease. It is very suggestive that central pneumonia, or pneumonitis, has been observed and broncho-pneumonic signs are present in half the cases. The disease is readily acquired in the laboratory and numerous cases have been reported. Encephalitis as a sequel to Q fever has been reported (Wegmann).

Findlay found that intranasal instillation of *C. burneti* (American and Australian strains) in mice causes interstitial pneumonia. These lesions are

similar in character to those produced by similar applications of the rickettsiæ of louse-borne and murine typhus.

Diagnosis.—An agglutination test with suspensions of rickettsiæ grown on egg-sac is now employed and is highly specific. Agglutinins are present in the serum for several months after an attack. A complement-fixation test was perfected by Bengtson. By this means it has been shown that in blood donors in Kent 3·29 per cent. gave positive reactions and in the Romney Marsh area unexplained febrile patients during the years 1949–1953 in 16·3 per cent. were, in effect, suffering from Q fever. The illnesses occurred between March and June during the lambing and shearing seasons.

Luoto (1953) has described a capillary agglutination test for cattle which possesses a high degree of simplicity, rapidity and reliability. The antigen is prepared from yolk-sac cultures of *C. burneti*, purified with ether, differentially centrifuged and stained with a modified Harris hæmatoxylin stain. Stock preparations keep indefinitely and when lympholysed it is kept at 40° C. The capillary tubes are 9 cm. long with an internal bore of 0·4 mm. One third of each tube is filled with antigen suspension by capillary action: the remainder filled with the serum to be tested. The end point is easy to read. Diagnosis can also be made by isolation of the organism in mice and guinea-pigs, or by feeding ticks on the patient and by subsequent transmission to mice. Neither the sera of patients, nor that of infected monkeys and rabbits, agglutinates *Proteus* OX19, OX2, or OXK. Radiographs of the lungs show evanescent diffuse opacities in the central portion and hilum. Derlinger described segmented or lobar consolidation in chest skiagrams in the great majority of cases; nevertheless recovery is rapid and complete.

Differential Diagnosis.—The fever has to be differentiated from atypical pneumonia, influenza, central pneumonia and psittacosis. The presence of "cold agglutinins" may assist in diagnosis from virus pneumonia.

Treatment.—The majority of modern antibiotics are curative in Q fever. At first streptomycin was used as Huebner and colleagues had found it especially effective in treatment of guinea-pigs infected with *C. burneti*. Chloromycetin by the mouth has been generally acknowledged as specific, but recently terramycin (oxytetracycline) is rated as even better.

Prophylaxis.—Burnet and Freeman found that the virus, when mixed with immune serum or treated with lauryl sulphate, confers immunity after inoculation, and so also do suspensions of rickettsiæ killed by heat or treated with formalin. The appearance of fever in abattoir workers has now been explained as due to handling meat of infected cattle. It is therefore obviously important that all meat workers should be protected by prophylactic inoculation. In the European outbreaks prevention is difficult because there is no contact infection, but it arises from a common source, such as dust. The rickettsiæ have been found in the faeces of ticks and other insects.

IX. RICKETTSIALPOX (VESICULAR RICKETTSIASIS): KEW GARDENS SPOTTED FEVER

This curious rickettsiasis was described by Huebner and Armstone in 1946 in inmates of an apartment house in New York with a pox-like rash. Within the next three years nearly 500 cases had been reported—all in New York City. The initial lesion resembles that of mite typhus and the rash is similar to that of other members of this group, except that vesicles occur. A case has been reported from French Equatorial Africa (de Gac and Giroud, 1951) as *rickettsiose vesiculeuse*.

The incubation period is about seven days and the temperature rises on the tenth after infection. The lesion starts as a small erythematous patch and soon a vesicle appears with centre developing into an eschar with enlargement of the corresponding lymph glands. Malaise and headache are invariably present. Fever lasts one to seven days. The rash appears on the second day in the form of discrete erythematous, maculo-papular spots, 2–10 mm. in diameter, all over the body. The mucous membranes are seldom involved and the hands and soles of the feet escape.

At a later stage the vesicles are replaced by blackish crusts which drop off leaving pigmented spots. This disease has no mortality. The lesions of smallpox, though initially similar, in their deeper and firmer character, have a different maturation.

The causal agent is *Rickettsia akari* which is transmitted by the mouse-mite, *Allodermanyssus sanguineus* (Hirst). *Bdellonyssus bacoti*, another murine parasite, is also capable of transmission under laboratory conditions. The rickettsia are extracellular, intracytoplasmic and intranuclear.

The domestic mouse is undoubtedly the reservoir and they have been found carrying infected mites, whilst they themselves have been proved to be immune. The Weil-Felix reaction is negative, but complement fixation tests, with ether-extracted soluble antigens, are reliable, giving a rising titre response. Reactions with Rocky Mountain fever antigens are positive also. (A good general account of this rickettsiasis has been written by Greenberg and Pellitteri, 1952.)

Treatment with aureomycin, 2–4 grm. daily, has been successful, whilst oxytetracycline (terramycin) is also effective.

Prophylactic Inoculation of the Typhus Group. Killed louse-borne typhus vaccine.—The earliest and most widely used method was that of Weigl. This vaccine is prepared from the intestinal contents of lice injected *per rectum* with suspensions of living *Rickettsia prowazekii*. After an interval the lice are killed and the intestines removed and ground up with dilute formol-saline. This method was employed in Poland and in Germany before the second world war. Considerable numbers of lice—between 200 and 300—are required to immunize a single individual, and the cost is great.

Killed tick-typhus vaccine.—A method in which the tissues of infected *Dermacentor andersoni* are used has been employed by Spencer and Parker since 1925 in vaccination against Rocky Mountain spotted fever; 150,000 people had been inoculated by 1935, and Parker (1941) stated that amongst persons infected within one year the mortality was

only 8.11 per cent. as compared with 82.85 per cent. amongst unvaccinated controls. Similarly, Monteiro (1938) has used the tissues of infected *Amblyomma cajennense* as a vaccine against São Paulo typhus.

Other cultural methods.—The chief difficulty lies in obtaining rickettsiæ in large enough numbers. Numerous methods have been used: e.g., rickettsiæ have been grown in serum with Tyrode's fluid containing chick embryo tissues, but the growth, which is at first luxuriant, cannot be maintained. Cox devised a method of injecting rickettsia (from typhus, Rocky Mountain spotted fever, *fièvre boutonneuse* and Q fever) into the yolk sac of the developing chick embryo, which yields a rich growth. Formolized or carbolized suspensions obtained by this method have been used in Spain and extensively during the civil war. By this method one dozen eggs yield 100 ml. of vaccine, enough for about thirty people.

Cox's vaccine can be produced in large quantities. The virus is grown in developing fowl embryo and is transferred to other fertile eggs by 0.5 ml. of 5–10 per cent. suspensions of yolk sac in 50:50 mixture of sterile beef infusion broth, or by using an equal quantity of undiluted yolk fluid. The latter method is preferred for the preparation of vaccines. The maximum multiplication is not usually obtained before 4–6 passages. Formolized suspensions of the rickettsiæ are then prepared, and have been found to be stable on storage. The vaccine is injected three times (0.5 ml. once and 1 ml. twice) at five-day intervals.

The customary methods so far employed as a means of testing the efficacy of typhus vaccines are active immunization of guinea-pigs, agglutination tests for *Proteus* OX19, and neutralization of antibodies in the serum of inoculated subjects.

The protection afforded seems to be only partial. Van den Ende and others (1948) published a report of an outbreak of murine typhus in twelve laboratory workers who had been immunized previously with Cox's vaccine. The infection was contracted by the respiratory route. The disease was moderately severe in three cases; mild in others.

It is recommended that two doses each of 1 ml. be given subcutaneously at intervals of 10–14 days. Thereafter a *booster* dose of 1 ml. should be given at the beginning and in the middle of the typhus season; as this vaccine contains egg protein, protein sensitivity must be watched for.

During the second World War efforts were made to produce an efficient vaccine for scrub typhus in Burma. Fulton and Joyner (1945) produced a mouse-lung preparation from mice and cotton rats which protected animals, but was never tried out in the field. Plotz and others (1946) prepared an inactivated tissue culture scrub typhus vaccine from peritoneal exudate of infected mice on yolk-sac culture which was suitable for mass production and protected against 5,000 to 32,000 M.L.D.'s of *R. tsutsugamushi*.

Subsection D.—FEVERS CAUSED BY BACTERIA

CHAPTER XII

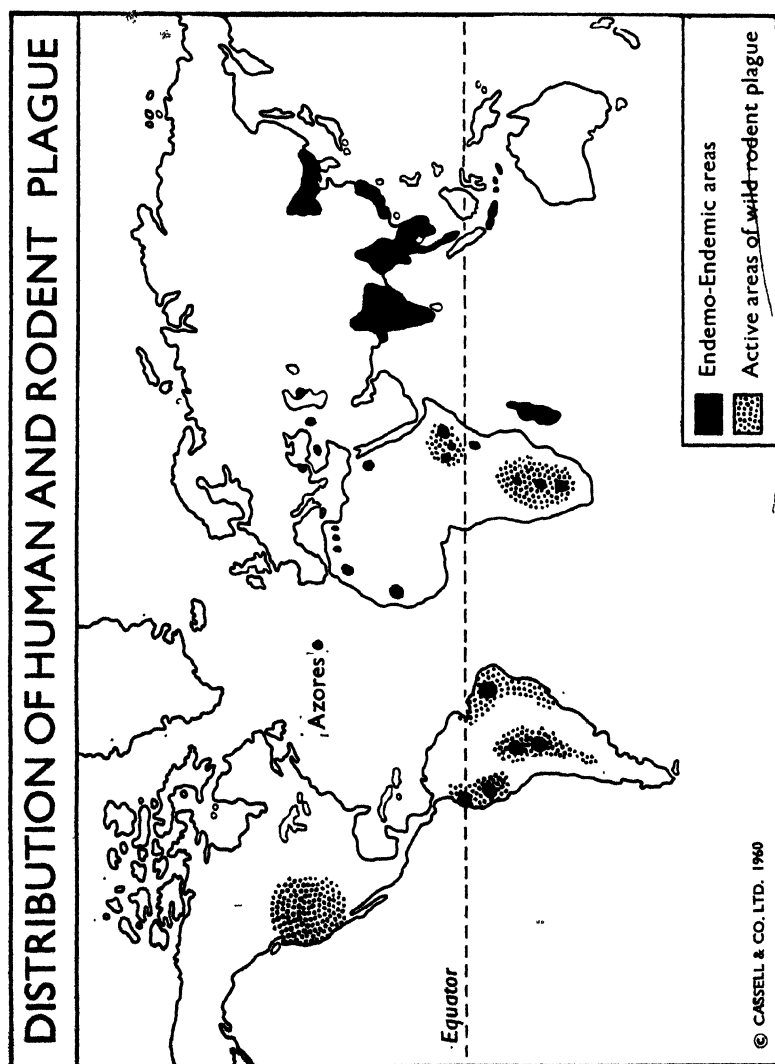
PLAGUE

Definition.—Plague is a specific, inoculable and otherwise communicable epidemic disease common to man and many of the lower animals. It is characterized by fever, adenitis, a rapid course, a very high mortality, and the presence of a specific bacterium, *Pasteurella pestis* (*Bacillus pestis*), in the lymphatic glands, viscera, and blood. In a large proportion of cases buboes form in the groins, armpits, or neck. The reader is referred to "The Conquest of Plague" (Hirst, 1953) and also to R. Pollitzer, W.H.O. Monograph Series, No. 22, 1954. Geneva. Plague is essentially a typical zoonosis (*see* p. 274).

Geographical distribution.—Probably plague is always present in some part of India and in Uganda, especially among the rude hill-people. It is known to have been endemic in the south-west of China, in the province of Yunnan, for many years. The extension of plague probably had its origin in that part of China, and it is safe to prophesy that it may continue endemic in that country for many years to come. Japan and the Philippines were both infected from China.

Imported from Hong Kong, the disease appeared in 1896 in Bombay other parts of India, where it still prevails. Soon after its appearance in India, plague became extensively epidemic in Mauritius and it still prevails there at certain seasons. Mombasa and British East Africa (including Nairobi), the West African countries, Madagascar, Delagoa Bay, Cape Town, Port Elizabeth, and Durban, also Sydney and Brisbane in Australia, and Alexandria in Egypt have all been invaded. Plague was introduced into Java in 1910, and has existed ever since in one of the most densely populated areas in the world. There has been an average of 3,000 to 6,000 cases *per annum*.

Until its appearance in Brazil, Argentina, and other South American countries, in San Francisco and Mexico, plague had never invaded the Western hemisphere; now it is of considerable importance in California. Peru, into which the disease was introduced from India in 1908, was the first country on the West Coast of South America to be invaded. The infection reached Ecuador through Guayaquil and raged at an altitude of 10,000 feet. Active foci of plague are now restricted to (1) Asiatic countries such as India, Burma, Thailand, Indo-China, Indonesia and China; (2) African countries, Azores, Morocco, Senegal, Kenya, Tanganyika, Belgian Congo, Madagascar, S. Africa; (3) S. American countries, Peru, Bolivia, Argentina. Selvatic plague tends to spread in N. and S. America and S. Africa (Map V).



Epidemiology and endemiology.—*Age, sex and occupation* have very little influence in plague. The youngest children are susceptible.

Atmospheric temperatures, if very high or very low, seem to have a repressing effect. On the other hand, plague on more than one occasion has flourished during a Russian winter. On the whole, the evidence points to moderate temperature—50° to 80° F.—combined with a certain degree of dampness as being the principal atmospheric condition favouring epidemic outbreaks and recurrences. In Hong Kong, for instance, it was found by Uttley that a mean temperature of 68° F. with a relative humidity of 88° and aqueous vapour tension of 0·500 favours the spread of plague, but when the temperature reaches 82–88° F. or more, for three to four months, with a vapour tension of 0·900, this disease tends to die out.

In large towns and in some districts in which plague recurs for several years in succession there is a seasonal periodicity (which may not be the same in all places) of maximum and minimum prevalence.

The *duration of epidemics of plague* is very variable. In large cities—Bombay, Hong Kong, Canton, for example—the disease, when fairly established, may not relax its grip for ten or more years. In smaller towns it may disappear in a few months.

The *extension of plague epidemics* is peculiar: the disease follows trade routes, and especially the grain trade. Sometimes it may spread rapidly from point to point; more generally it creeps slowly from one village to another, from one street or one house to another. Sometimes it skips a house, a village, or a district. In former times it was spread in the Mediterranean by cotton and woollen goods (Hirst, 1958).

The most convincing early experimental evidence on the transmission of plague by fleas was described by Dr. James Lowson in Hong Kong in May, 1898 (Simond's paper was published in October 1898). He clearly demonstrated (1) presence of plague bacilli in fleas from plague rats, cultures and inoculation into healthy rats and guinea-pigs; (2) transmission of plague by fleas from infected rats and applying them to healthy rats.

ÆTIOLOGY

The micro-organism.—The specific cause of plague is the bacillus which was discovered by Yersin and Kitasato in 1894. It occurs in great profusion in the characteristic buboes, generally in pure culture, and is present, also, in great abundance in the spleen, intestines, lungs, kidneys, liver and other viscera and, though in smaller numbers, in the blood, while in the pneumonic type it is found in the sputum in profusion. It may be found also in the urine and fæces. Towards the termination of rapidly fatal cases it occurs in great numbers in the blood.

*Pasteurella*¹ *pestis* (Fig. 52) as seen in a blood-film or in preparations from any of the other tissues, is a short, thick cocco-bacillus (1·5 to 2 by 0·5 to 0·7 μ) with rounded ends, very like the bacillus of chicken cholera. A capsule, or the appearance of one, can generally be made out, especially in bacilli in the blood. The organism is readily stained by aniline dyes, especially by Romanowsky stains, the extremities taking on a deeper colour than the interpoler part, giving a bipolar appearance.

¹ Has also been named *Yersinia pestis* (Davignat).

Bhatnagar states that virulent stains of *P. pestis* can be recognized by the abundance of the envelope substance.

It is non-motile, Gram-negative, indol-positive, and gives nitrite reaction with sulphanic acid and X naphthylamine.

Cultural characters.—When sown on blood-serum and kept at body-temperature

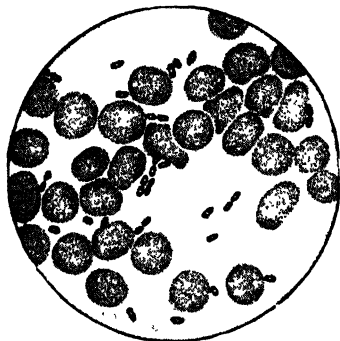


Fig. 52.—*P. pestis* in peripheral blood in septicæmic plague. $\times 500$.
(Microphotograph: Dr. J. Bell.)

in from twenty-four to forty-eight hours an abundant moist, yellowish-grey growth is formed without liquefaction of the culture medium. On agar, but better on glycerin-agar, the growths have a greyish-white appearance. In agar plate cultures they show a bluish translucence, the individual colonies being circular, with slightly irregular contours and a moist surface; on mannite-neutral-red-bile-salt agar the colonies are bright red, but are colourless on a similar medium in which lactose is substituted for mannite. Litmus-milk and glucose-broth are rendered slightly acid; lactose-broth is unchanged. Young colonies are glass-like, but older ones are thick at the centre and more opaque; they are singularly coherent and may be removed *en bloc* with a platinum needle. Stab-

cultures show after one or two days a fine dust-like line of growth. Cultivated on broth in which clarified butter or coco-nut oil is floated, *P. pestis* presents characteristic stalactite growths which gradually fall off, forming a granular deposit. Examined with the microscope, these various cultures show chains of a short bacillus, presenting here and there large bulbous swellings. In gelatin the bacilli sometimes form fine threads, sometimes thick bundles made up of many laterally-agglomerated bacteria, and involution forms are common. The bacillus does not produce spores.

The most favourable temperature for culture is 28° C.

The bacillus of plague can be modified by artificial methods; it is well known that some process of this kind takes place in nature, for as a plague epidemic decreases, so the case-mortality falls.

Modern bacteriologists recognize varieties of *P. pestis*.

- (a) Glycerol-negative known as *P. pestis* var. *oceanica* or *P. pestis orientalis*.
- (b) Glycerol-positive *P. pestis* var. *continentalis* which some observers regard as comprising two sub-varieties:—*P. pestis* var. *antiqua* produces nitrous acid in broth, and *P. pestis* var. *mediævalis* which does not produce nitrous acid.

Repeated passages through a commensal host can cause a change from mediæval to oceanic variety of *P. pestis*. Further, Devignat thinks that plague in Ituri (Belgian Congo) is caused by a variety—*P. pestis antiqua*. Another feature is virulence. There is difficulty in producing virulent mutants from an avirulent strain. Virulent strains seem to present a significantly greater catalase activity than do avirulent strains. The antigenic structure of the plague bacillus has been studied by chemical as well as by serological methods. Rowland found that the plague bacillus is built up by two varieties of protein:—

one soluble in distilled water or saline:

the other insoluble and possessing no antigenic or toxic properties.

Experimental plague.—In the guinea-pig, within a few hours of the introduction of the bacillus, a considerable amount of œdema appears around the puncture, and the adjacent gland is perceptibly swollen. At the end of twenty-four hours the animal is very ill; its coat is rough and staring; it refuses food, and presently becomes convulsed and usually dies on the third or fourth day. If the body is opened immediately after death a sanguineous œdema is found at the point of inoculation, with hæmorrhagic inflammatory effusions around the nearest lymphatic gland which is much swollen and full of bacilli. The intestines are hyperæmic; the adrenals, kidneys, and liver are red and swollen. The much-enlarged spleen frequently presents an eruption of small whitish granulations resembling miliary tubercles. All the organs, and even any serous fluid that may be present in peritoneum or pleura, contain plague bacilli. In the blood, besides those free in the liquor sanguinis, bacilli are found in the mononuclear, though not, it is said, in the polymorphonuclear leucocytes.

Rôle of the rat in plague.—Although small and circumscribed epidemics of plague may occur without the intervention of the rat, as



Fig. 53.—Common sewer rat (*Rattus norvegicus*). (London School of Hygiene and Tropical Medicine.)



Fig. 54.—Black rat (*Rattus rattus*). (London School of Hygiene and Tropical Medicine.)

when it first appeared in Colombo, there can be no doubt that in most epidemics of the bubonic form this rodent plays an important part, both in the introduction and in the spread of infection. The species principally concerned are *Rattus norvegicus* (or *decumanus*), the grey rat, and *Rattus rattus*, the black rat (Figs. 53 and 54). The mouse, *Mus musculus*, is also susceptible.* The bandicoot and musk rat are of little importance in these respects, although susceptible to laboratory infection. In Bombay the epizootic appears first in the *Rattus norvegicus* community, *Rattus rattus*—the more domestic species—being subsequently attacked. Later the disease appears in epidemic form in man (Chart 13).

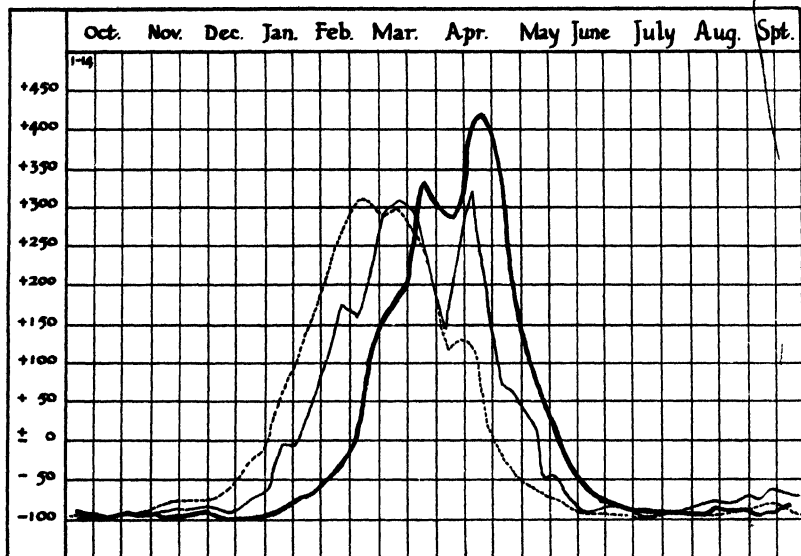


Chart 13. Showing progress of plague in rats and man.
 ("Report of Indian Plague Commission.")

..... Infected *R. norvegicus*.
 ——— Infected *R. rattus*.
 ——— Human deaths from plague.

The seasonal prevalence of bubonic plague in rats is marked and is not due to a periodicity in their reproduction, but is connected with periods in which fleas are most numerous. In places in which plague epidemics keep recurring year after year the local rats acquire a considerable degree of immunity; moreover, this is transmitted hereditarily. Thus, in plague-free towns in India—e.g. Madras and Dacca—the mortality among the local black rats experimentally infected was 100 per cent., while in plague-stricken towns, such as Cawnpore and Poona, it was much less.

Other animals may die of plague during an epidemic; dogs are said to be immune.

In Uttar Pradesh Indian research workers have discovered that a gerbille—*Tatera indica*—harbours the infection in its underground burrows

during periods between outbreaks of human and rat-plague. They pass the bacillus to *R. rattus* and the latter transmits it to man through the fleas they both carry.

History.—Although the main credit is given to the Indian Plague Commission for the part it played in elucidating the transmission from rat to man, yet it is an astonishing fact that the pioneer studies of P. L. Simond (*Ann. Inst. Pasteur*, 1898) have been forgotten and his conclusions neglected, for now it appears that many of the generally accepted facts of plague were enunciated by him for the first time. That it is primarily a disease of rats was recognized by Yersin and Roux in 1897 and the rôle of fleas as vectors of the infection suggested by Ogata in the same year, but it was Simond who, after a brief visit to India, found that the outbreak of plague in rats was followed by an epidemic in man; furthermore he found plague bacilli in fleas and noted that the primary lesion in man was often a blister containing plague organisms. He noted that fleas leave the body of a stricken rat and found that the bacilli could be conveyed by the bite of a flea. He tried out the mouse-protection test as a measure of the efficacy of anti-plague serum and finally suggested sulphuric acid fumes as a means of rat destruction in ships.

Sylvatic (syntatic) or wild rodent plague.—It is now realized that plague exists in a smouldering state over vast tracts of territory among the Asiatic marmots; among the "susliks," mice and jerboas of the desert region of south-eastern Russia; among the gerbilles and *muridae* of the African high veld and coastal region; among the chipmunks and ground-squirrels of California; and in South America among the cavies ("cuis," wild guinea-pigs), and other peculiar rodents of the Pampas. In Chile, on the other hand, plague is restricted almost entirely to rats in the seaports. Desert country is unfavourable to the rat flea, *Xenopsylla cheopis*. Although field-rodent plague has given rise so far to comparatively little human mortality in most countries, in North Manchuria, where the disease is endemic in the giant marmot or "tarabagan," virulent epidemics of *pneumonic plague* have occurred.

In Central Africa and Madagascar *domestic* rodents are the chief reservoir, and in S. Africa wild-rodent plague prevails. In the Argentine plague again is confined to wild rodents; in Brazil only *domestic* rodents are concerned. Recently wild-rodent plague has been discovered in Kurdistan and in Turkey. In Kenya, Heisch has found definite foci of wild-rodent plague. In view of the rapid fall in numbers of human plague it appears probable that wild-rodent reservoir of infection may soon constitute the main problem, and that man is rarely and accidentally infected.

The reservoir host is defined as man in the definitely established foci of plague, but other families or subfamilies, species or subspecies of animals, are also found infected and play a subsidiary role, though, when living near man, are able to act as intermediaries.

Rôle of the marmot and other rodents.—Mongolian and Siberian pneumonic plague epidemics are associated with the occurrence of the disease in species of marmot known as "tarabagan" (*Arctomys bobac*, Fig. 55),¹ and several smaller species (*Citellus citellus*, *C. pygmaeus* and *C. mugojaricus*), locally known as "susliks," which can harbour the plague

¹ A subspecies of *A. bobac*, *Arctomys centralis*, was found infected in the Narinak epidemic of 1929-30.

bacillus in their bodies without apparently suffering any ill effects during hibernation, thus constituting a more or less permanent reservoir of the plague virus. Possibly plague infection is transmitted to man by the fleas which infest these animals, but it is more generally considered that the rodent fleas play a minor part and that the infection is transmissible via the alimentary tract. It has been shown that in hibernating spermophiles *P. pestis* loses its virulence and is less easily cultivated. Epizoötics of plague in these regions generally begin after hibernation.

The pouched marmot of the Caucasus (*Spermophilus guttatus*) is extremely susceptible to plague infection and is probably concerned in the spread of the disease in that region. In Transbaikalia plague occurs in *Spermophilus eversmani* and in *S. dauricus*, which are 22 cm. long and rather resemble the tarabagan. The presence of spermophiles, which are related to marmots and ground-squirrels, can be determined by the characteristic excrement at the mouth of their burrows.

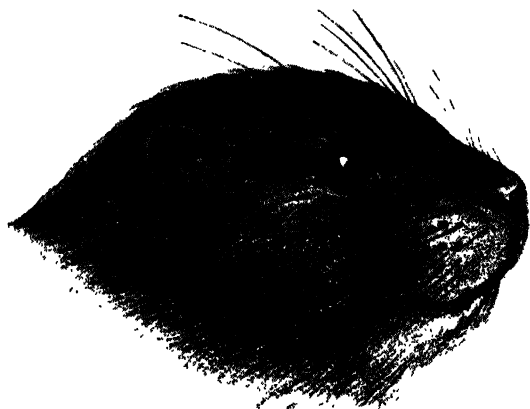


Fig. 55.—*Arctomys bobac*, Siberian marmot
(nat. size).

In South-East Russia, from October, 1925, to May, 1927, there were 42 plague epidemics with 810 cases. The infection of 11 of these originated from domestic and field mice, four from spermophiles, three from jerboas (*Dipodipus sagita*), and four from gerbilles (*Rhombomys opimus*), while seven outbreaks were traced to infection at slaughter of plague-infected camels. Fleas capable of biting man were found on nearly every rodent and they play an active part in the spread of plague in Russia. Proventricular blocking (see p. 259) with the plague bacillus occurs in the gerbille fleas (*Ceratophyllus tesquorum* and *C. lœviceps*), also in *Oropsylla silantievi*, the flea of the Tarabagan (*Arctomys bobac*), which sticks in the fur and is found in pelts, and *Ceratophyllus tesquorum*, and *Neopsylla setosa* which infest "susliks."

Plague is known to exist in the seven western states of America, but it has not so far been noted east of Wyoming nor south of Utah, save in

California; the most northerly point is some 150 miles north of the Californian border. In California the ground-squirrel (*Citellus beecheyi*, Fig. 56), although it does not live near human habitations, infects rats that do, and thereby acts as an important reservoir of *P. pestis*.

In addition to *C. beecheyi*, six species of ground-squirrel are now known to harbour plague including *C. fisheri*, *C. grammurus*, and *C. townsendi*. Other wild rodents from which plague-infected fleas have been collected include tree-squirrels (*Sciurus douglasii*, *Xerus erythropus*), chipmunks (*Tamias sp.*), marmots (*Marmota flaviventer nosophora*, *M. fl. engelhardti*) prairie dogs (*Cynomys parvidens*), and a field-rat (*Arvicanthus rufinus*). Eskey and Haas have pointed out that wild rodent plague in the Western United States is not always accompanied by infection of domestic rats.

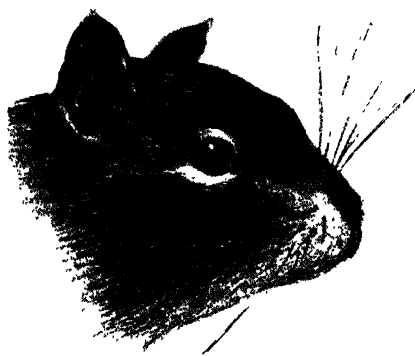


Fig. 56.—*Citellus beecheyi*, ground-squirrel of California (nat. size).

In 1947 rodent plague was reported from six Western States, but once one fatal case in man in California. In New Mexico, Link found evidence of plague only in prairie dogs (*Cynomys mexicanus*) and marmots (*Marmota flavirostris*) or their fleas, but no human cases had been reported. In California the infection is spread from the ground squirrel to the rat and from rat to rat by the fleas (*Diamanus montanus*, *Hoplopsyllus anomalus* and *Ceratophyllus acutus*). In Washington State, U.S.A. *Lagurus curtatus*, a vole inhabiting sage brush, has been found to be an important reservoir. In the Southern States two species of wood or pack-rat are reservoirs—*Neotoma cinerea*, a bushy-tailed species in forest-country, and *N. desertorum*, the round-tailed species found in the southern deserts.

In South Africa, especially in the Cape Province, the rodents of the inland veld have become infected with plague and, by continuously passing the disease from one to another, constitute a persistent and dangerous source of human infection. On the high veld the gerbilles (*Taterona lobengulae* and *Desmodillus auricularis*), the ground-squirrel (*Geosciurus capensis*), and the multimammate mouse (*Mastomys coucha*, or *natalensis*)

are the most important—the last forming a link by conveying infected fleas from gerbille burrows into human habitations. This is a fertile, inactive, lazy mouse which occupies burrows deserted by gerbilles. In the lower bush country the striped mouse (*Rhabdomys pumilio*) plays the chief rôle, while the springhaas (*Pedetes caffer*), a giant jerboa, on account of its extreme mobility, is capable of widely disseminating plague. Two carnivores, the suricate and the yellow mongoose, are susceptible to plague by feeding on dead and dying rodents, and it has been pointed out by Mitchell that the discovery of gerbille remains in the fæces of these animals is a valuable indication of the existence of a rodent epizootic in the veld districts, as these animals do not normally eat them unless they are sick.

The gerbilles, especially the Namaqua species (*D. auriculatus*), range both within and without the plague area and extend throughout Africa to the Sahara. *Tatera brantsii* ranges from the E. Karoo, the high veld, Kalahari, and of Natal, *T. schinzi* from the Kalahari and its borders; but *T. afra* is not found in the enzootic areas. The flea vector is *X. eridos*, whose chief host is *T. brantsii*.

South African rodents harbour a large number of species of flea capable of transmitting plague:

- Discopsyllus lypsus*—Striped mouse, Karroo rat.
- Chiatopsylla rossi*—Namaqua gerbille, Lobengula gerbille.
- Xenopsylla brasiliensis*—House rat, multimammate mouse.
- Xenopsylla cheopis*—House rat.
- Xenopsylla eridos*—Striped mouse, Karroo rat.
- Ceratophyllus fasciatus*—House rat.
- Xenopsylla hirsuta*—Lobengula gerbille.
- Ctenocephalus canis*—House rat, dog, hare.
- Leptopsylla musculi*—House mouse and rat.

In North Africa spontaneous plague is found in the following rodents: *Psammomys rondairei*, *Dipodillus dodsoni*, *D. campestris*, *Gerbillus hirtipes* and *Meriones shawi*. In Uganda the rodent reservoir is *R. rattus*, originally it was *R. mastomys Coucha ugandæ* and *X. braziliensis* is the chief vector.

In Dakar (Senegal) a shrew (*Crocidura stampflii*), on the Gold Coast, the giant rat (*Cricetomys gambianus*), and in Kenya the field-rat (*Arvicanthus abyssinicus*) play their part in the dissemination of plague.

In South America, in the Argentine pampas, Uriarte and Villazon have shown on several occasions that rodents of the cavy type suffer in plague epizootics. The species specially concerned are *Microcavia australis* and *M. galea*; a cricetid also, *Graomys griseoflavus*, has been shown to be experimentally very susceptible. It is arboreal but has become semi-domesticated, nesting in the roofs of houses, and recently de la Barrera found a small outbreak of human plague which was traced to this animal and to two species of *Eligmodontia* and a rodent *Holochilus balnearum*. In Venezuela *Heteromys anomalus*, together with *Sigmodon hirsutus*, are incriminated as primary plague reservoirs; the latter is really a forest species, but they both enter houses in search of food.

On observations such as these the modern quarantine against plague has been framed.

Rôle of the flea in plague.—It is now known that plague is not

communicable from animal to animal by simple contact, but is readily communicated by fleas, and principally by *Xenopsylla cheopis* (Fig. 448, p. 1086), the rat-flea of the tropics, *Ceratophyllus fasciatus*, the rat-flea of temperate climates, and *Ctenocephalus canis* and *C. felis*, which bite men, dogs and cats indifferently. These act as passive intermediaries and carriers of the bacillus. *P. pestis* multiplies in the stomach of the flea, retaining its virulence for over twenty days and is then passed out in the fæces, so that the flea serves not only as a carrier, but also as a multiplier of the germs. Wu Lien Teh has shown that in outbreaks of plague in Manchuria the human flea (*Pulex irritans*) may convey the bacillus direct from patient to patient without the intervention of the rat.

Especially convincing are the experiments of the Indian Plague Commission, which clearly showed that, if fleas are excluded, healthy

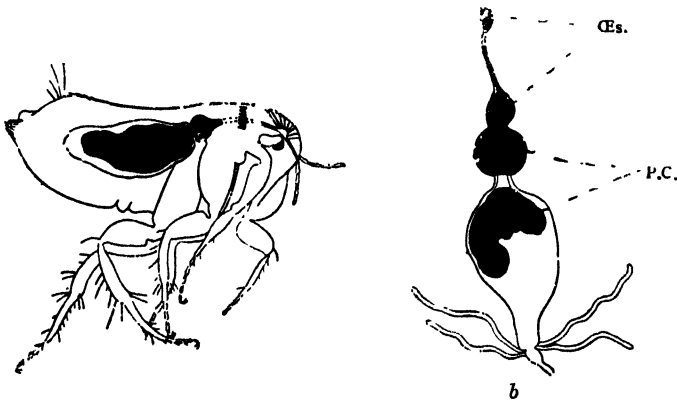


Fig. 57.—*a*, Flea viewed as a transparent object; the proventriculus and stomach contain a mass of plague-culture. *b*, Flea's stomach, obstructed by growth of plague-culture.

Cs., Distended oesophagus containing fresh blood; P.C. obstructing mass of plague-culture. This figure illustrates the method of transmission of *P. pestis* by *Ceratophyllus fasciatus*. (By permission of Sir C. J. Martin, "Journ. of Hyg.," 3rd Plague Suppl., Jan., 1914.)

rats will not contract the disease, even if kept in intimate association with plague-infected rats. Young rats may even be suckled by their plague-stricken mothers and remain healthy. It suffices to transfer fleas from a plague-infected to a healthy animal, or to place the latter in a room in which plague rats had died recently and had been subsequently removed. The fleas that have left the body of the dead rats, remaining in the room, convey the bacillus. An animal placed on the floor cannot be infected, if the precaution is taken to surround the cage with "tangle foot," so as to keep off the fleas; but if it be placed on the unguarded floor, either in its cage or allowed to run about, or even if suspended 2 in. above the floor—a distance not beyond the saltatory powers of the flea—it will become infected.

Martin and Bacot found that a proportion of the fleas fed on plague-infected rats develop a peculiar condition of stomach and oesophagus,

which become blocked with blood-clot containing a pure culture of *P. pestis*. When such a flea feeds on a normal rat, part of the culture regurgitates and communicates infection; at the same time bacilli are passed in the faeces and may infect through any existing abrasion. They further observed that the "blocked" fleas died very rapidly, apparently of thirst, if placed in a warm, dry atmosphere (Fig. 57). There is apparently little difference between wild rodent and domestic rat fleas in the readiness of infection. The life-span of the infected flea is comparatively short, about 3.2 days.

In temperate climates fleas are most numerous during the warmer weather; hence, summer and autumn are the bubonic plague seasons. In warm climates bubonic plague is most likely to become epidemic when temperature ranges between 10° and 30° C.—temperatures favourable to the multiplication and activity of the flea. Temperatures over 30° C. are unfavourable, especially if the atmosphere is dry.

The flea, then, communicates plague either by its fouled mandibles, by regurgitation, in the act of sucking, or by provoking scratching and consequent inoculation of the bacilli deposited in its faeces.

The capacity of a flea's stomach is about $\frac{1}{2}$ c.mm. and in most cases of human bubonic plague there are not sufficient plague bacilli in the peripheral blood-stream to infect it with any regularity, except in the terminal stages of fatal cases. The "cheopis index" is regarded as important by sanitarians, i.e., the number of fleas per rat. An index of over 5 is likely to produce an outbreak of bubonic plague.

It has long been known that large tracts of country and important cities in India, such as Madras, have remained immune from plague, though in constant communication with plague-infected centres. In 1914 Rothschild and Jordan pointed out that the rat-fleas of Indian cities belonged to three closely allied species—*X. cheopis*, *brasiliensis*, and *astia*—and soon afterwards Hirst and Cragg discovered that in those districts, in which plague was uncommon, *X. astia* replaced *X. cheopis* as the common ectoparasite of the rat. From this and other experimental evidence it is now assumed that this species is unable to convey the plague infection in the same manner as *X. cheopis* (see p. 1085). *Pulex irritans*, the human flea, though important probably in the middle ages, does not nowadays play a dominant role.

X. cheopis can flourish in northern countries in superheated houses and factories, as in U.S.A. and Russia, even during the winter months.

Bionomics of the rat-flea.—In ordinary circumstances the rat-flea completes its developmental cycle in from fourteen days to three weeks, but in warm damp weather this may be shortened to ten days. It requires ideal tropical conditions for propagation. The average life of a flea, separated from its host, is about ten days, but it is capable of remaining alive without food for two months, should the temperature of the air be low. In tropical temperatures the insect can harbour the plague bacillus without feeding on blood for forty-five days and can survive in cotton goods.

Apart from the very serious danger arising from vermin infected with chronic plague, which may hang about a house, the house itself does not retain the infection for any length of time. The Plague Commission has

shown that floors of cow-dung contaminated with *P. pestis* do not remain infective for more than forty-eight hours and that floors of "chunam" cease to be so in twenty-four hours.

Evidence of rat-mortality is not always conspicuous, even when the epizootic is severe. Dead rats may not be found in the open, but many may be discovered if search is made in the right places. Black rats which live in the roofs of native houses usually fall down on to the floor when stricken with plague.

Pathology.—After death from plague the surface of the body very frequently presents numerous ecchymotic spots or patches. The number and extent of these vary, apparently, in different epidemics. In some epidemics the cutaneous hæmorrhages have been both extensive and numerous. The characteristic buboes are generally apparent; occasionally there are also furuncles, pustules, and abscesses. Rigor mortis is usually moderate; sometimes post-mortem muscular contractions, like those in cholera, take place. Post-mortem rise of temperature is often observed. Decomposition is said to set in early.

The characteristic appearance of plague in a necropsy is that of engorgement and hæmorrhage, nearly every organ of the body participating more or less. There is also parenchymatous degeneration in most of the organs. The brain, spinal cord, and their meninges are markedly congested, and there may be an increase of subarachnoid and ventricular fluid. There are numerous and pronounced puncta cruenta on the brain sections; occasionally there may be considerable extravasations of blood into the substance of the brain (mesencephalon and medulla oblongata).

Ecchymoses are common in all serous surfaces; the contents of the different serous cavities may be sanguineous. Extensive hæmorrhages are occasionally found in the peritoneum, mediastinum, trachea, bowel, stomach, pelvis of kidney, ureter, bladder, or in the pleural cavities. The lung frequently shows evidences of bronchitis and hypostatic pneumonia; sometimes hæmorrhagic infarcts and abscesses are found. The right side of the heart and the great veins are usually distended with feebly coagulated or fluid blood. In pneumonic plague the superficial lymphatic glands are not enlarged; the pleural cavities contain blood-stained serum; the infected lungs are deeply congested and œdematous, and at a later stage pneumonic consolidation is found. The bronchi contain blood-stained serum, and the bronchial glands are swollen and hæmorrhagic.

The liver is congested and swollen, its cells are degenerated and may be the seat of miliary plague abscesses. The spleen is enlarged to two or three times its normal size. The kidneys are in a similar condition. The mucosa of the alimentary canal as a whole is congested, showing here and there punctate ecchymotic effusions and, occasionally, hæmorrhagic erosions, and even—especially about the ileo-cæcal valve—ulcerations.

The lymphatic system is always involved; around the glands there is much exudation and hæmorrhagic effusion, with hyperplasia of the gland-cells and enormous multiplication of plague bacilli.

Symptoms. *Incubation period.*—Symptoms of plague begin to show themselves after an incubation period of from 2–8, rarely 15 days.

The average case of plague: prodromal stage.—In a certain but small proportion of cases there is a prodromal stage characterized by physical and mental depression, anorexia, aching of the limbs, feelings of chilliness, giddiness, palpitations and sometimes dull pains in the groin at the seat of the future bubo.

Pestis minor, or ambulatory stage.—Abortive or ambulatory cases of

bubonic plague have been reported in connection with almost every true outbreak of the disease and in some constitute a high proportion. Clinically these cases present mild, general febrile symptoms with a bubo, and when that suppurates the temperature falls, and the patient recovers. The diagnosis may be difficult because the plague bacillus may be very scanty in the pus. The differential diagnosis has to be made from climatic bubo (*Lymphogranuloma venereum*).

From the clinical aspect, plague in man can be divided into the following varieties :— (1) Bubonic (2) Septicæmic (3) Pneumonic and (4) Meningeal.

Bubonic plague (zootic plague).—This is the most common form and constitutes about three-quarters of the total number. The incubation period is usually very short; generally within twenty-four hours the characteristic bubo, or buboes, develop. According to Pollitzer (1945) it is possible to distinguish three varieties of bubonic plague: (1) well-marked bubonic infection not leading to secondary septicæmia, (2) bubonic affection followed by secondary septicæmia, (3) serious general septicæmia combined with slight affection of lymph glands. Generally (in 70 per cent.) the bubo appears in the groin, especially on the right side and affecting one or more of the femoral glands; less frequently (20 per cent.) the axillary; more rarely still (10 per cent., especially seen in children) the submaxillary lymphatic glands may be the seat of the bubo, while the tonsil may be the primary focus of infection. In rare instances cervical buboes may actually result. Buboes are usually single, but in about one-eighth of the cases they form simultaneously on both sides of the body. Very rarely buboes form in the popliteal, epitrochlear, or clavicular glands. Occasionally they develop simultaneously in different parts of the body. A curious point, noted in North West America, is that in squirrel-conveyed plague axillary buboes are common. Plague buboes vary very much in size. Sometimes they are not as large as a walnut; in others again they may be as large as a goose's egg. Pain may be very severe, but sometimes it is hardly felt. Besides the enlargement of the gland there is, in most instances, considerable pericellular infiltration and œdema.

Stage of fever.—The stage of invasion may last for a day or two without serious pyrexia, but usually it is much shorter, or it may be altogether absent. The disease usually develops abruptly, without a definite rigor or other warning, the thermometer rising rapidly to 103° or 104°, or even to 107° F., with corresponding acceleration of temperature and pulse. The temperature usually falls after three or four days and then rises again. The skin is now dry and burning, with bloated face; the eyes congested, sunken and staring; hearing is dulled. The tongue is swollen, covered with thick creamy fur, which dries rapidly and soon becomes brown or almost black. Sordes form on the teeth and about the lips and nostrils. Thirst is intense; prostration extreme, whilst from utter debility the voice is reduced to a whisper. Sometimes there is wildly fatuous delirium, or it may be of the low muttering type.

Coma, convulsions—sometimes tetanic—retention of urine, subsultus tendinum and other nervous phenomena ensue. Vomiting is in certain cases very frequent. Some patients are constipated, but in others there

is diarrhoea. The spleen and liver are usually enlarged. Urine is scanty, but rarely contains more than a trace of albumin. The pulse at first full and bounding, in the majority rapidly loses tone, becoming small, frequent, fluttering, dicrotic and intermittent. In the later stages the heart is usually dilated, the first sound being feeble or absent altogether. Hæmorrhages are seen on the mucuous membranes in severe cases. There is usually a polymorphonuclear leucocytosis.

Stage of recovery.—In favourable cases, sooner or later, after or without the appearance of the bubo, the constitutional symptoms abate with the setting in of profuse perspiration. The tongue begins to moisten, the pulse-rate and temperature to fall, and the delirium to abate. The bubo, however, continues to enlarge and to soften. After a few days, if not incised, it bursts and discharges pus and sloughs—sometimes very ill-smelling. In rare instances suppuration is delayed for weeks; whilst in some the bubo subsides after a few weeks, or perhaps months, without having broken down. The sores left by the buboes and abscesses of plague are extremely indolent and may take months to heal. Owing to contracture and fibrosis of lymphatic tissue, œdema of the leg on the affected side usually supervenes.

Skin affections.—In a very small proportion of cases what are usually described as carbuncles, in reality small patches of moist gangrenous skin that may gradually involve a large area, develop on different parts of the integument. These occur either in the early stage or late. Sometimes they slough and lead to extensive gangrene.

Kirk and Crawford have described a generalized papular rash on the hands, feet and pectoral region. Should life be continued sufficiently long, the vesicles become converted into pustules resembling smallpox. These observations confirm in a remarkable manner, as MacArthur has pointed out, the old writers who described manifestations, in the Plague of London of 1665, as “blains.”

Complications.—Occasionally a pyæmic condition, with boils, abscesses, cellulitis, parotitis, or secondary adenitis, succeeds the primary fever. During convalescence tragic sudden cardiac failure is not uncommon. Secondary pneumonic plague with blood-stained sputum may supervene, but the patient may recover.

Hæmorrhages of different kinds are not an unusual feature of plague—ecchymotic effusions of a purplish or dull-red tint, varying in size from a hemp-seed to half an inch in diameter. These are found frequently in certain malignant epidemics.

Abortion almost invariably occurs in pregnant women; the fœtus sometimes shows signs of the disease.

Death may take place at any time. Usually it occurs between the third and fifth day, with symptoms of profound adynamia, heart-failure, or perhaps from convulsions, from coma, from internal hæmorrhage or, later, from exhaustion consequent upon prolonged fever or suppuration, or from secondary hæmorrhages.

Septicæmic plague, or pestis siderans.—In this type there is no special enlargement of the lymphatic glands during life, although after death throughout the body they are somewhat enlarged and congested. The

high degree of virulence and the rapid course of the disease depend on the entry of large numbers of the bacilli into the blood, where they can be readily found during life. The patient is prostrated from the outset; he is pale and apathetic; there is generally little febrile reaction (100° F.). Great weakness, delirium, picking of the bed-clothes, stupor and coma end in death on the first, second, or third day, or, it may be, later. Frequently in these cases there are hæmorrhages.

It is probable that in many cases of bubonic plague there is some degree of septicæmia, and that in a minority of cases this may progress to the full septicæmic type, or may give rise to plague pneumonia.

Pneumonic plague (Demic plague).—This occurs frequently in epidemic form among the marmot-trappers of Northern China, who live under very insanitary conditions, but may occur spontaneously wherever the bubonic form is found. It is especially dangerous to the patients, attendants, and visitors, because of the multitude of bacilli which are scattered about in the patient's expectoration, because the clinical symptoms are unlike those of typical plague and are apt to be mistaken for some ordinary form of lung disease. The illness commences with rigor, malaise, intense headache, vomiting, general pains, fever, and intense prostration. In the early stages there may be little to suggest pneumonic plague, except the marked discrepancy between the almost negligible physical signs and the gravity of the patient's condition. Cough and dyspnoea set in, accompanied by a profuse, watery, blood-tinged sputum. The sputum is not viscid and rusty, as in ordinary pneumonia. From the outset clouding of consciousness is very marked. Moist râles are audible at the bases of the lungs, the breathing becomes hurried; other symptoms rapidly become worse, delirium sets in, and the patient usually dies on the fourth or fifth day. This is the most fatal as well as the most directly infectious form of plague. Epidemics of 50,000 and more cases have occurred in Manchuria, where the plague bacillus exists as an intestinal infection in the marmot which acts as a reservoir. Pneumonic plague has been recorded from Nigeria, Ghana, Ecuador, New Orleans and elsewhere. In these countries hæmorrhage into the intestinal canal occurs in about 8 per cent. of plague-infected rats and the organism is passed out in the fæces; in this manner the plague bacillus can be disseminated in dust and inspired by man directly into the lungs. (Connal and Paisley.) Murdock believes that secondary plague pneumonia occurs in a proportion of patients with bubonic plague and that the disease is then spread by droplet infection and inhalation. Pneumonic plague is exceedingly dangerous to nurses and others in contact with the patients.

It has been pointed out by Kellog that, whereas in rat-borne plague pneumonia is rare, in squirrel plague it is the reverse.

Meningeal plague.—Primary plague meningitis was found in Dakar by Lafont and colleagues, by Williams from East Africa and by Devignat from the Congo, by Pollitzer, Landsborough (1947) and others from Chunchow, South China, and S. California (Meyer). From South America cases have been reported by Lastra and Rodeiro (1944). In all except the first named meningeal involvement was a complication

of the bubonic form from the ninth to seventeenth days. In clinical features it rather resembles cerebro-spinal meningitis with painful headaches, stiff neck and Kernig's sign. Special symptoms are meningeal irritation, convulsions, vestibulo-cerebellar symptoms and coma. Primary plague meningitis is a pyrexial illness with meningeal irritation, from which *P. pestis* is obtained by lumbar puncture. The cerebrospinal fluid is under pressure and yellow in colour closely resembling that of acute suppurative meningitis. The initial infection is probably due to droplet spread. The brain shows congestion and flattening of sulci and is covered with a thick fibrinopurulent exudate.

Mortality.—The mortality is usually greatest at the beginning and height of the epidemic. The death-rate may be anything from 60 to 95 per cent. of those attacked. Much appears to depend on the social condition of the patient and the attention and nursing available. Thus, in a Hong Kong epidemic, while the case-mortality among the indifferently fed, overcrowded, unwashed, and almost unnursed Chinese amounted to 98.4 per cent., it was only 77 per cent. among the Indians, 60 per cent. among the Japanese, and 18.2 per cent. among the Europeans—a gradation in general correspondence with the social and hygienic conditions of the different nationalities. In the South American epidemics and in the circumscribed epidemics in Europe the mortality was only about one-third of that in India and China. Pneumonic plague was generally fatal in from three to four days. Van den Berg and Vos report that in an epidemic in Java (1930), in 66 cases of plague, the mortality was 76 per cent. The sixteen who recovered had all been suffering from bubonic plague. The chances of recovery were somewhat better in men than in women. In this series there were 57 cases of bubonic plague, two of plague ulcers, 29 of septicæmic plague, and one of primary plague pneumonia.

Diagnosis.—Fever and adenitis during a plague epidemic must invariably be viewed with suspicion, and particularly if the fever rapidly assumes an adynamic character. In the early stages diagnosis may be very doubtful, especially in pneumonic plague, and in the countries of high filarial endemicity in which filarial adenitis is common. Blood-culture was recommended by Onoto, by inoculating blood into broth containing 1 per cent. of sodium citrate. Rosier stated that in Java splenic puncture is valuable in establishing a diagnosis and is not opposed by the native population. Junior and de Albuquerque described an allergic skin test for which an emulsion of infected guinea-pig lymph gland was used. In Western America the differentiation of mild cases of plague from tularæmia is important (p. 277), but the discovery of the bacillus in the glands, blood, sputum, or discharges is the only thoroughly reliable test. Should a cocco-bacillus be found with the characteristic bipolar staining, it should be cultivated by Haffkine's method in broth on which clarified butter (ghee) or coco-nut oil is floated. In case of doubt, animal inoculation should be used; a little of the virus from the patient or a culture is rubbed into a shaven area (1 in. square) on the abdomen of a white rat or a guinea-pig. *P. pestis* inoculated in this

way kills the guinea-pig in seven days, the rat sooner and white mice in forty-eight hours. The latter may be inoculated at the root of the tail.

Post-mortem indications of plague in the rat.—Before rats suspected of being plague-infected are handled, they should be immersed in disinfectant to destroy ectoparasites.

The lymphatic glands should be first exposed. If the rat is infected, subcutaneous infection around the glands is generally recognizable. If the gland is itself inflamed, this is almost diagnostic of plague; the liver will be yellow, sprinkled with innumerable pinky-white granules. The spleen is enlarged, congested, and occasionally granular. The serous membranes are of dull lustre with petechial or diffuse hæmorrhages. Serous, or blood-stained serous effusions are present in 72 per cent. of such rats; if, on microscopical examination of scrapings from glands or spleen, bipolar-staining bacilli are detected, the case is probably plague. Too great stress must not be laid on bipolar staining alone, as this feature depends somewhat on the method; it is best demonstrated by the Leishman eosinazur stain. *P. pestis* persists for a long period in the bone marrow of plague rats, even after putrefaction has set in.

P. pestis, *P. pseudotuberculosis rodentium*, *P. suisepitica* and *P. aviseptica* closely resemble each other and are scarcely distinguishable by the usual cultural methods, but the latter two have no "envelope substance," though they have a common antigen with *P. pestis*. None coagulates milk, but in agar *P. pestis* produces a more glistening membranous growth. *P. pseudotuberculosis rodentium* produces a clear, yellowish growth on potato. On Drigalski medium it produces blue colonies: *P. pestis* reddish ones. *P. pseudotuberculosis* readily associates itself with the production of smooth and rough colonies with all degree of transitions between them. The smooth colonies show closest association to *P. pestis* and are the most virulent. *P. aviseptica* produces indol and does not reduce methyl red. In cases of doubt some assistance is afforded by the fact that *P. pseudotuberculosis* has not been found in Central Africa, China, Indo-China and Madagascar.

The most satisfactory means of differentiation is animal inoculation. Rabbits, guinea-pigs, and white mice are susceptible to *Pasteurella pseudotuberculosis*, but white rats are not. The Indian Plague Commission laid stress on the latter point, as these animals are instantly killed by *P. pestis*. These organisms belong to the hæmorrhagic septicæmia group. Gunnison and colleagues differentiate these organisms by bacteriophage.

Rodent plague and fleas.—In the investigation of rodent plague the inoculation into animals of pooled fleas is important. Cyanide gas is the best method of collecting fleas from rodents. The long bones of rodents may be sent to the laboratory for culture tests of marrow.

Differential diagnosis.—Bubonic plague has sometimes to be distinguished from other affections associated with enlarged glands, such as streptococcal infections, *lymphogranuloma venereum*, filarial adenitis, and occasionally from an anthrax pustule.

In filarial and streptococcal infections lymphangitis tracks are usually visible, but in bubonic plague there is usually no visible sign of the primary infection. In glandular fever the cervical glands are as a rule primarily affected and there is an excess of heterophil antibodies in the serum (goat's corpuscle test).

Generalized pustular plague has to be differentiated from chickenpox or smallpox; carbuncular plague may be mistaken for anthrax;

septicæmic plague may be confused with typhus and subtertian malaria. In the United States, North Europe and Russia, tularemia may resemble plague.

Pneumonic plague differs from other forms of pneumonia in three main characteristics: (1) The patient is extremely prostrated, although his critical state can hardly be accounted for by such physical signs as are present in the chest; but by the time definite involvement of the lung can be demonstrated, he generally dies. (2) The sputum is watery, never thick, and soon becomes very blood-stained. (3) Pleural effusion is usually present in plague pneumonia.

Treatment.—If it be deemed advisable to attempt to lower the temperature, sponging the body every hour with warm water is a much safer measure than antipyrin and similar drugs. The buboes in the early stage may be treated with applications of glycerin and belladonna.

Sulphonamides.—Durand, Girard, Schütze and others showed that certain sulphonamides, especially sulphapyridine, protect mice infected with plague, if combined with anti-plague serum.

Antibiotics.—*Streptomycin* exerts an action on *P. pestis* comparable with that on *Br. tularensis*. It has been tried out experimentally on mice and inhibits the growth of *P. pestis in vitro* in concentrations of three units. When injected subcutaneously in mice it gives an 85 per cent. survival rate in doses sufficient to kill 100 per cent. of control animals. It is also effective in curing artificially produced plague pneumonia in guinea-pigs (Herbert, 1947).

The first two human cases were treated with streptomycin at Buenos Aires (1947), and though the prognosis appeared hopeless, the patients survived. This miraculous result has now been confirmed (1948) by Karamchandani and Rao (1948) in five moribund patients at Antapur, Madras. Streptomycin, 0.5 gm., was given intramuscularly six-hourly for 72–96 hours up to a maximum of 8.0 gm. Since that time recoveries even from pneumonic plague have been reported by Lewin and colleagues (1948) in doses of 1.8 gm. of streptomycin daily for 8 days, with a total of 24 gm. of sulphadiazine. On the ninth day the temperature fell to normal and plague bacilli could no longer be found in the sputum.

Combined treatment.—Wagle believes that sulphadiazine is the best of the sulphonamides, but that streptomycin constitutes the most effective drug. Recent reports indicate that a combination of these powerful drugs is the best. Wagle and Bedarkar obtained five cures in six patients suffering from pneumonic plague with intramuscular streptomycin (0.66 gm. every four hours), anti-plague serum and *sulphamerazine*.

General prophylaxis. Quarantine.—Modern systems of land or sea quarantine directed against plague take cognizance of the facts that the incubation period of the disease may extend to ten days, and that plague may affect certain of the lower animals as well as man. Ten days is the minimum period that should elapse from the time of departure from an infected place, the date of the last death, or the arrival of a ship or batch of travellers with cases of plague among them, before granting free pratique.

The eradication of rats from ships requires special measures. Sulphur dioxide may be used in concentration of 2 per cent., either as 8 lb. of roll sulphur or 4 lb. of liquid sulphur dioxide per 1,000 cubic feet. In the Clayton system, which has never been extensively used in British ports, sulphur is burned in a furnace and the gas propelled by fans throughout the ships.

Hydrogen cyanide is being more extensively employed. Under proper supervision it is comparatively safe and has decided advantages over sulphur, as it does not tarnish metals or damage articles. Hydrogen cyanide diffuses slowly. Small amounts which may be absorbed are rapidly evolved and oxidised on exposure to air or during cooking. Hydrogen cyanide may be generated either by pumping liquid HCN from cylinders or by throwing glass ampoules into holds, or from outside by the Glen Liston apparatus. "Discoids," wood pulp discs saturated with $\frac{1}{2}$ oz. HCN, may be used. Calcium cyanide dust (known in the trade as Calcid or Cyanogas) in a dusting apparatus will dislodge rats from deck fittings and lifeboats, or may be blown as a fine powder through a rubber tube behind panellings.

For fumigation the ship is divided into sections each of which is measured by volume. Water-bottles and cabin water-tanks are emptied, moist food removed and mattresses turned on edge. All apertures are sealed. Danger boards are prominently displayed. Ships may be fumigated loaded or unloaded. A plague infected ship should be treated before unloading.

When plague breaks out in a small village community, as soon as the disease is recognized, measures should be taken to prevent the inhabitants leaving the locality and thus disseminating it. There is little danger of this until the inhabitants become alarmed by a rapid extension of the disease. If possible, after the patients have been isolated in a special hospital, the village should be evacuated for a month. The safest and most thorough form of disinfection is by fire, and in an isolated village prompt burning of the infected houses is the surest method of stamping out the infection. The clothes and bedding of all patients should be burned. The dead should, with as little delay as possible, be buried in deep graves or cremated. Isolated observation camps should be organized, in which "suspects" and "contacts" may be segregated for a time equal at least to the incubation period of the disease. War should be waged against all rats and mice, and their corpses burned. This is specially important in rat-infested quarters of Eastern towns, bazaars, grain stores, go-downs, etc.

In an outbreak in a town, it must be borne in mind that plague, once established in human beings, is communicable to others and to rats by the expectoration, and by discharges from the buboes or glandular swellings; and that a plague in rats usually precedes plague in human beings. The main efforts should be directed towards destruction of rats by methods detailed on pp. 272-274.

After death the rat is treated with Flit or soaked in lysol. Smears are made from lymph glands, liver and spleen, and stained by Leishman. Broquet's

medium (calcium carbonate 2; glycerine 20; distilled water 80 parts) is a good preservative for fleas and permits isolation of *P. pestis* after six days.

For the detection of plague-infected houses, guinea-pigs, which do not harbour fleas as a rule, are turned loose in warehouses as convenient traps for rat-fleas.

In India the compulsory inspection of all dead bodies before burial has been found a valuable measure for discovering infected houses and localities.

Destruction of vermin and other measures in anticipation of the introduction of plague bacilli.—The campaign against rats is usually carried on by rat-traps and rat-catchers, and the cautious laying down of poisons (see p. 273). The pumping of SO_2 gas under pressure is useful for warehouses. So long as the sulphurous-acid gas is dry, and not used on damp articles, no damage is done to merchandise. Care has to be taken with damp things, as they may get discoloured.

Where possible, houses and warehouses should be made rat-proof—not an easy measure, considering the burrowing and climbing habits of the rat. *Rattus norvegicus* can penetrate ordinary lime-mortar or soft brick, but is stopped by cement and concrete. Its burrows may attain a depth of 18 in., but *Rattus rattus* is not so active in this respect. Simpson recommended that walls should be at least 6 in. thick, when made of hard brick or concrete, and that they should extend to not less than 18 in. below the level of the ground floor, and the latter should be paved with concrete 3 in. thick, covered with $\frac{1}{2}$ in. of cement. All ventilators should be protected with iron gratings, and all openings around wires and pipes cemented. In New Orleans some warehouses are elevated, leaving a clear open space beneath: in others an impervious wall is built around the ground floor, penetrating 2 ft. into the ground. In a third, and a most effective type, the ground floor is laid out in concrete with a protective wall round the edges sinking 2 ft. into the ground. The mooring cables of ships should be shielded in such a way as to prevent egress or ingress of rats, and all gangways should be taken up at night or when not in use. Native food-stores are, as a rule, set out on poles and can be protected from rat-invasion by suitable wooden discs.

In South Africa rigorous measures have been adopted by the Health Department to prevent the spread of rodent plague; it has endeavoured, apparently with success, to place a gerbille-free belt between the mountain range and the sea. Gangs, working under departmental rodent officers, employ two main methods—poisoning and gassing. The poisoning is effected by dropping strychnine-impregnated grain into gerbille burrows. Near homesteads, a Capex cartridge is lighted, plunged into a burrow and the opening closed with earth. Meyer has shown that methyl bromide, sprayed at the rate of 10 c.c. per burrow-opening, is efficient in controlling burrowing rodents and their fleas. Care, however, must be taken in its application.

Prophylactic measures based on a consideration of the flea fauna. Control of DDT and insecticides.—Spraying with water emulsion of DDT of walls and ceilings of farmhouses and other buildings has proved efficient in control of rat fleas. Nicholson and others by dusting with DDT in the holes and haunts of rats have caused the reduction by 80 per cent. of the

numbers of *X. cheopis* and other fleas. Hill, by dusting rat runs and hiding places in Georgia with 10 per cent. DDT in pyrophyllite, has shown that a significant reduction occurred in the numbers of *X. cheopis* and *Leptopsylla segnis*. Nicholson and Gaines (1950) could not detect any significant degree of recovery on the part of the flea population three months later. Within a week of application of 5 per cent. DDT powder to rat burrows and runs in shops, warehouses in S. Carolina, the fleas were almost completely eliminated from rats. (For use of rat poisons see Warfarin, p. 272.)

These methods have recently been improved by Kartman and Lonergan (1956) which are especially applicable to wild-rodent plague. The "metal hood type of DDT bait-box" is one made of aluminium sheeting, or tin plate, about 20 ins. long, 7 ins. wide and 5 ins. high. Both ends are open, except that just inside each a flat sack of 20 × 20 mesh serim netting filled with 10 per cent. DDT powder is suspended in such a way as to form a screen against which the rat has to brush when entering the box to reach the bait which is placed in a container on the floor of the box. When entering and leaving the box the rat becomes dusted with the powder, both on the back and on the belly, so that it carries some DDT to its burrow. In Hawaii where the bait box was tested the flea index was very low, but the diminution of the number of *X. cheopis* within a period of two months suggested that it might be possible to reduce the index to a level at which transmission of plague amongst wild rodents would cease. They also found that these boxes can be used for rat-control at the same time as flea control by the use of Warfarin-poisoned bait. A combined operation such as this is most successful.

Personal prophylaxis.—All unnecessary visits, either to plague patients or plague neighbourhoods, should be, if possible, prevented. Attendants on the sick ought to take care that the ventilation of the sick-room is thorough, that cubic space is abundant, and that the utmost cleanliness is practised. Nurses must not hang over patients unnecessarily; they must also be careful to seal up and cover any wounds, no matter how trifling, on their own hands. Stools and urine must be disinfected, and hands frequently washed. To obviate risk from wounds and to prevent the access of fleas, those engaged on plague duties should wear boots and have the legs protected by trousers tied tightly round the ankles or, better, by puttees.

The attendants on pneumonic cases should provide themselves with masks of muslin, three- or four-fold, changed when at all damp, and also with goggles to protect the eyes. In Mukden a mask of absorbent cotton-wool (16 by 12 cm.) enclosed in muslin, and retained in position by a many-tailed gauze bandage, together with goggles, rubber gloves, and cotton uniform, proved thoroughly effective.

Prophylactic inoculation. *Haffkine's inoculation* consists essentially in subcutaneous injection of six-weeks'-old cultures of plague bacilli incubated 25–30° C. and killed by heat—65° C. for one hour; carbolic acid 0·5 per cent. then added; up to 4 ml. is injected according to the size and age of the individual. In the inoculated the incidence of plague is 8 per 1,000 of the population concerned, whereas it is 34 per 1,000 in the uninoculated in the same com-

munities; the case-mortality in the inoculated was 39·5 per 100 attacked: in the uninoculated 78 per 100. The best results are obtained from a two-months' growth of *P. pestis* which has been stored about eighteen months. It needs great care in its preparation. Its storage in hermetically sealed bottles should be insisted upon, and every bottle ought to be tested before use. The resulting reaction is sometimes severe. The efficacy of the vaccine depends upon the virulence of the bacilli composing it; cultures made from non-virulent strains are useless. The potency of plague vaccine is enhanced by the incubation of plague cultures at 37° C. in place of 26° C.

Those in attendance on plague patients should receive 20 ml. of Yersin's anti-plague serum, and 3 ml. of Haffkine's vaccine on the same day; ten days later a second dose of vaccine should be given. Attendants should wear lysol-impregnated gowns fastened at the wrist, ankles and neck, rubber gloves and gum-boots. They should not shave, but they should disinfect themselves and their clothes daily.

Prophylactic inoculation with *avirulent living plague bacilli* was practised in Java by de Vogel and Otten. The smooth variety on culture has been used as antigen, and 400,000 persons were immunized in this manner without incident or accident. The plague strain "tjiwidej" was discovered by accident, and is so avirulent that both rat and guinea-pig can withstand a whole culture when inoculated. Animal experiments show much better immunity with this living vaccine than that obtained with dead cultures. Otten's method was commenced in 1935 and up to 1939 total injections numbered 9,286,287. Excellent results have been obtained and the present decline in the epidemic is attributed chiefly to this vaccine. The mortality in the vaccinated fell to about 20 per cent. It has been proved possible to obtain a plague strain with combined properties of avirulence and immunogenic power. These two properties do not necessarily coincide.

DESCRIPTION OF THE COMMONER SPECIES OF RATS CONCERNED IN THE SPREAD OF PLAGUE

The spread of plague and epizootics amongst rats seems to be primarily by the fierce *R. norvegicus*. The more delicate *R. rattus* receives its infection from the former, the sewer rat. Both these species are pestigenic. When the rat dies the fleas desert the body and seek a new host; thus if a sewer rat (*R. norvegicus*) dies in the basement, the fleas attach themselves to the black house rat (*R. rattus*), and are spread to human beings.

Terms employed.—Rodents which are capable of being infected with plague are divided into *pestiferous* and *pestigenic*; thus the common mouse is a pestifer, but is not ordinarily a transmitter. *Selvatic* (or *sylvatic*) plague is the plague of the hinterland. In North Africa, for instance, plague of the "bled" of Tunisia has been regarded as selvatic and due to desert rodents; further south in the Sahara a mouse (*Psammomys rondairei*), though predominant and a very susceptible animal, has hitherto not been affected.

An intimate knowledge of the appearance and habits of the many species of rats is hardly necessary to the tropical specialist: considering the important rôle several species play in the spread of plague he should, however, be able to identify the more domestic varieties. For this purpose the following Table, contributed by M. A. C. Hinton, will be found useful:

Rattus rattus, Linn.—The black rat. Build slender; muzzle sharp; ears large, translucent, cover eyes when folded down; tail usually long, never much shorter than head and body; coarse hair on rump; hind foot (heel to tip of longest toe, without claw) 35–40 mm.; weight of adults rarely more than 8 oz. Indigenous, wild, more or less arboreal in Indo-Burmese countries. In tropics generally dominant domestic rat in houses and ships. The chief domestic races are distinguished as follows:

A. Back reddish or greyish-brown.

a. Under parts pure white or pale lemon. *R. r. frugivorus* Raf. (= *tectorum*). Common in Mediterranean region. *R. r. kijabius*. Uganda.

b. Under parts darkened.

a¹. Ventral hairs with rusty tips. *R. r. rufescens* Gray. Common rat of Indian houses.

b¹. Ventral hairs without rusty tips. *R. r. alexandrinus* Geoff.

B. Back black; under parts dusky or slate-grey. *R. r. rattus* Linn. Essentially a domestic form which has been evolved in cold temperate countries.

N.B.—The black rat tends to be brown in the tropics.

The forms *frugivorus*, *alexandrinus*, and *rattus* have now acquired an almost world-wide distribution; *frugivorus* is the least, *rattus* the most modified race. These are climbing rats, common on ships; frequent in dwellings in warm countries, and not shunning man; they are of especial importance as plague-carriers; attain sexual maturity early (min. weight sex-mature = 70 gm.); breed throughout the year; gestation about 21 days, but with concurrent lactation about 31 days; litter of from 4 to 11; average litter 5 or 6.

Rattus norvegicus, Berkenhout (= *decumanus*).—The brown, grey or sewer rat. Robust; muzzle blunt; ears small, opaque; tail noticeably shorter than head and body; fine hairs on rump; hind foot 40 to 45 mm.; weight of adults commonly 17 oz., often much more; colour brown or grey above, silvery below. A melanic form (often confused with *R. rattus*) quite common.

RAT DESTRUCTION (DERATIZATION)

Terriers may be used, the rats being driven out of their holes by flooding from a watercart. Cats are useful, but they are susceptible to plague. Traps of all description are of value, and rats readily enter a funnel-shaped trap showing a light at the far end. Runs may be made with double closing doors, or gins or nipper traps may be placed in the path of rat-runs. One man can attend to 100 to 200 traps a day. In towns and ports where plague exists, 40 to 50 traps should be set per day per 1,000 inhabitants. Rats which are caught alive must be asphyxiated and then combed for fleas. The flea is placed for twenty-four hours in pure phenol to make it transparent, so that species and sex may be determined. The total number of fleas divided by the number of rats gives the "flea-index."

RODENTICIDES

Warfarin easily takes first place for combined safety and effectiveness. Water-soluble warfarin can be used in addition to the solid bait. Warfarin-treated oats, a commercial anti-coagulant rodenticide is composed as follows:

Warfarin = 0.025 per cent., white mineral oil 11.0 per cent., *p*-nitrophenol 0.25 per cent. and rolled oats 88.78 per cent.

RODENTICIDES

	RECOMMENDED STRENGTH BY WEIGHT	RELATIVE SAFETY	RELATIVE EFFECTIVENESS
Warfarin	0.025%	2	2
Red Squill	5-10%	1	7
ANTU	2-3%	3	6
Zinc phosphide	1%	4	5
Arsenic trioxide	3%	5	4
Thallium sulphate	0.5%	6	3
Sodium fluoroacetate (1080) ..	—	7	1

Sorexa warfarin (3 (2-acetyl-1-phenylethyl)-4-hydroxy-coumarin) has none of the disadvantages of poison. It acts slowly and creates no suspicion in rats; it kills without pain; is virtually harmless to humans and domestic animals, but continues to act until all rats are exterminated. Sorexa (1 per cent. warfarin in fine oatmeal) kills rats by drastically reducing the clotting power of the blood and by causing leaks in the small capillary vessels. This leads to extensive internal hæmorrhages which are rapidly fatal. It possesses the peculiar ability to inhibit the formation of prothrombin which is produced in the liver and this clotting is a vital factor. When the total dose is divided into several smaller ones, it is administered daily over a period of several days when fatal hæmorrhages are produced. The principle has been introduced by multiple dosing whereby the rat feeds for several days before death occurs without warning or pain.

Tolerance cannot be established in a rat colony. The only rodent control methods which are satisfactory are those which can give complete clearance, remembering that rats breed at 3-4 months, averaging 8-6 litters a year with 8-10 young in each litter so it is obvious that with control measures at 80 per cent. efficiency repeated quarterly, the effects of control will be counterbalanced by reproduction.

Initial clearance is readily achieved by making available to all rats sufficient bait to satisfy the appetites of the whole infestation.

Reinfestation can be controlled by the use of permanent baiting point which attract the migratory rats.

Perimeter defence of premises by use of permanent or semi-permanent bait containers.

Bait.—Any bait that causes rats to feel ill is immediately suspect and the entire colony is warned against the bait. No prebaiting is necessary with sorexa. Ground cereals are used as a basis for bait. In U.K. it is medium oatmeal; in U.S.A. yellow corn meal, and in South Africa maize meal. Palatability is increased by the addition of 2-10 per cent. fine sugar or 1-2 per cent. refined vegetable oil. Good results are obtained if sorexa is dusted onto soft egg shells. When conditions are dry and warm and foodstuffs available with low moisture content, increased bait-take can be achieved only if water is placed near the dry bait.

Rules of bait replacement.—1. Lay many baits (4-6 ounces), wherever rats are known to run.

2. Inspect baiting points and replenish where bait is being taken.

3. Replenish bait as long as there are signs of feeding (7-14 days).

4. Maintain permanent baiting points to destroy any rats which may come into the cleared area.

The quickest clearance of rats is obtained where enough attractive bait is laid in the correct places. Mix sorghum—1 part to 19 parts of bait base.

Siting of the bait.—Rats are particular where they feed and while preferring quiet corners, they do not like feeling hemmed in. Rats like a quick and easy "get away," but feed in a draught or any open space. It is generally accepted that for every rat seen there are at least ten living in the area and enough bait must be laid for the whole colony. Rats will not eat food which is mildly rancid or made unpalatable.

GROUND SQUIRREL AND RODENT CONTROL (California and S. Africa)

General measures: (1) poison bait, (2) poisonous gases, (3) trapping, (4) shooting, (5) exclusion, and (6) encouragement of natural enemies (Storer). A poison, 1080, is used for ground squirrels and "prairie dogs"—1-2 oz. in 100 lb. of grain act best.

Gassing with carbon bisulphide is highly effective. Strychnine-coated barley is made as follows (the bitter taste being delayed by these means):—Barley 16 quarts; strychnine 1 oz.; sodi bicarb 1 oz.; starch paste $\frac{3}{4}$ pint; corn syrup $\frac{1}{4}$ pint; glycerine 1 tablespoonful; saccharine $\frac{1}{10}$ oz. Insecticides for control of plague vectors in the Californian ground squirrel are specially effective against the fleas—*Ctenocephalus felis* and against *Xenopsylla cheopis*. These are heptachlor, dieldrin, aldrin, B.H.C., chlordane, and parathion. Dieldrin is most effective when sprayed into each burrow at the rate of 0.64 grm. actual insecticide; by this method the flea index is reduced from 38 or more to 0.48 (Rickmay, Ames and Lindt 1954). In California and Western U.S.A., the abundance and variety of rodent fleas found in the nests of the burrowing owl (*Speotyto cunicularia*) suggests that this bird is a host and carrier of plague-infected parasites.

ZOONOSES

Plague represents a typical example of the evolution of a human disease from an infection originally confined to wild animals. Other examples are leishmaniasis, relapsing fever, the typhus group, yellow fever, trypanosomiasis (Chagas' disease, Rhodesian sleeping sickness) and virus encephalitis. From the valuable information obtained from interim ecological studies, a coherent pattern has emerged which provides a rational basis for the control of the diseases in question. The actual term—"zoonosis"—can be defined as an infection of man naturally acquired from other vertebrates, though the infection may be reversed when it may pass from

man to animals (Heisch, 1956). The importance is emphasized of the "holistic" or "synecological" approach to this problem. A complex is formed by the organism, the vertebrate, the vector, and various other features of the environment. This state is not static, but it is something new and may give rise to new combinations and an ever-changing epidemiological pattern. The ecological and epidemiological data on zoonoses are integrated into a doctrine of natural focal distribution, or "*Nidality*" of transmissible and infectious disease.

Zoonoses occur within geographical areas, the terrain of which is characterized by well-defined ecological peculiarities which are in turn determined by topography, climate, vegetation and other environmental factors. In such natural foci the pathogens, their vectors and vertebrate hosts, form an association or *biocenosis* within which the infection circulates independently of man as long as human beings do not come in contact with them, but when this happens the infection spreads to man and the wild animals become the reservoirs of the disease in question. Natural foci thus constitute a potential epidemiological danger and it is important that their existence and localization should be recognized beforehand. Therefore a knowledge of the geographical background or *terrain* (Pavlovsky's "landscape epidemiology") of the zoonoses is important.

In plague the importance of a resistant host is emphasized for the maintenance of a particular infection in nature. Certain wild rodents, like *Arvicanthus* or *Otomys* spp., generally act as good reservoirs of the plague bacillus which would soon disappear if it had to depend solely on the domestic rat or man. The former are termed "permanent," the latter "temporary" and each fills its different role. Only when all conditions exist which are necessary for the formation of such a zoonosis, is it possible for this state to exist, to be maintained and spread. The number of zoonoses at present known is very large, and about some of them our knowledge is extensive; of others fragmentary.

In Kenya, for example, permanent foci of selvatic plague are to be found in the foothills above the Rift Valley; especially also in India in the foothills of the Himalayas, but *not* in the cultivated plains below. A similar focal distribution is sometimes seen in scrub typhus (p. 229), trypanosomiasis, leishmaniasis, relapsing and yellow fevers (p. 319). Should conditions alter, as in the plains, the infection may flare up into an epidemic. Such unstable areas are now called "ecotones" and they may also be found at the margin of forests with their "fringe habitat." A *biocenosis* is distinctive of long association with a particular disease, as for instance, *miombo* (a deciduous woodland) with *rhodesiense* trypanosomiasis.

Every biocenose is influenced by other biocenoses, because none is a completely closed system. Thus a disease may occur in different kinds of biocenoses, for reasons which allow a species of animal to occur in more than one kind of biocenose. As a rule the distribution of a pathogen is wider than the disease caused by it (Audy, 1958).

Glossary of terms employed in zoonoses.

Association, biocenose, biome, community and ecosystem. are terms applied to types of natural assemblage by ecologists.

Ecosystem = unit of vegetation.

Species-network = entire mutually connected assemblage of species within the ecosystem.

Centres of action = local groupings of species as well as local concentrations of energy-exchange.

Ecological unit (Audy) = closely knit community of organisms.

Intra-specific = parasite carried wholly between individuals of host-species concerned.

Inter-specific, but obligatory = when the infecting parasite requires more than one species of host-organism to complete a life-cycle.

Inter-specific, but incidental = transmitted incidentally from some|other host species which maintains the parasite.

CHAPTER XIII

TULARÆMIA

Synonyms. Deer-fly Fever ; Pahvant Valley Plague ; Rabbit Fever ; Ohara's Disease.

Definition.—Tularæmia is a specific infectious disease of rodents, caused by *Brucella tularensis*, and is transmitted from these animals to man by the bite of infected blood-sucking insects, or by the handling or dissection of infected jack-rabbits and other rodents.

Geographical Distribution and Endemiology.—In American endemic areas the disease is most prevalent in the months of June, July, and August, when it is conveyed by a blood-sucking fly, *Chrysops discalis*, from one infected jack-rabbit to another. In Scandinavia and in Northern Europe most cases occur from July to October: in Southern Europe and Asia Minor from June to August. *Br. tularensis* has been isolated from nymphs and larvæ of the tick, *Ixodes ricinus*, taken from a hare in S. Norway (Kohls and Locker). Tularæmia is a disease of the rural population, particularly field workers, but it has also been recorded among dealers in rabbits who handle infected jack-rabbits, and those who prepare their skins for market. In 1924 Parker and Spencer found that the tick (*Dermacentor andersoni*) could act as a host and as vector of the disease in man and in rodents, and demonstrated that hereditary transmission takes place in it. They further showed that the rabbit tick (*Hæmaphysalis leporis-palustris*) acted as a vector from one rodent to another. Olin studied a serious outbreak of 115 cases in Sweden in 1937 which occurred especially among peasant women, who in summer-time go bare-footed and who are stung by numerous mosquitoes, and he considered that these insects may act as vectors. Although in the main an insect-borne disease, it may be water-borne. "Lemming fever" in Norway is tularæmia due to drinking water polluted by bodies and excreta of lemmings. In Montana, U.S.A., streams are similarly contaminated by beavers, and in Wyoming these animals have been found dead in large numbers from *Br. tularensis* infection. Ingestion tularæmia is contracted by eating insufficiently cooked flesh of an infected animal.

Ætiology.—*Brucella tularensis* is a small non-motile, Gram-negative organism, measuring 0.3–0.7 μ in length; when stained in the tissues it gives the appearance of being surrounded by a capsule. Though normally occurring as a rod-like structure, it frequently assumes a coccus shape. It stains best in tissue preparations with Giemsa's stain, but in smears from cultures it shows up well with aniline gentian-violet. On account of their small size some of the organisms pass through the coarser bacterial filters.

The organism is difficult to cultivate; it will not grow on plain agar or in bouillon, and, until recently, had been cultivated only upon the coagulated yolk of hen's eggs, but Francis succeeded in producing an abundant growth

upon serum-glucose-cystine agar. The cystine medium is inoculated with the heart's-blood of the infected animal, or a small piece of the liver or spleen is rubbed on the surface and allowed to remain in contact with the medium. Growth appears about the third day, and flourishes luxuriantly on subcultures without the addition of fresh animal tissue. To ensure the primary growth, it is necessary that a piece of animal tissue be added to the medium. Fermentation of glucose, lævulose, maltose and glycerine occurs, with acid formation.

Composition of cystine agar.—Cystine agar consists of beef-infusion agar, having a pH of 7.6, to which 0.02 per cent. of cystine is added, after which it is sterilized for fifteen minutes in a steam sterilizer, and subsequently incubated for twenty-four hours to ensure sterility.

Cultures of *Br. tularensis* are extraordinarily infectious, and should be handled with great care.

In its serum reactions cross-agglutination occurs in connection with *Brucella melitensis* and *Br. abortus*. About 23 per cent. of tularæmia sera do so, and about 35 per cent. of undulant fever sera agglutinate *Br. tularensis* to some degree. Concentrations of the organism are best obtained from emulsions made from the spleens of infected mice or guinea-pigs.

The organism is pathogenic for guinea-pigs, rabbits, white rats, mice, ground-squirrels (*Citellus beecheyi*), gophers (*Thomomys bottæ*), and *Macaca* monkeys; while brown rats (*R. norvegicus*), horses, calves, pigs, goats, cats, dogs, fowls and pigeons are found to be refractory. The organism can be transmitted by *Chrysops discalis*, as well as by the stable-fly *Stomoxys calcitrans*, the bed-bug, *Cimex lectularius*, the squirrel-flea, *Ceratophyllus acutus*, the rabbit-louse, *Hæmodipsus ventricosus*, and the mouse-louse, *Polyplax serratus*.

Ticks can also act as vectors—i.e., *Dermacentor andersoni*, *D. variabilis*, *D. occidentalis*, *Ixodes ricinus*, var. *californicus*, Banks, and the rabbit tick (*Hæmaphysalis leporis-palustris*). Four species of mosquito, *Aedes* and *Theobaldia*, have been shown to transmit *Br. tularensis* under experimental conditions. In Sweden *Aedes cinereus* does so in nature.

Dermacentor andersoni is particularly important, *Br. tularensis* being found in the intestinal lumen, in the cells of the gut wall, in the body fluids, and in the fæces. The organism is harboured throughout the winter months and infection is transmitted to the eggs of the tick.

The disease occurs as a natural infection in wild rodents, especially in rats, field mice, hares and rabbits. Burroughs, Holdenfried and others have given a complete list (1945). In the *United States*: The wandering shrew, grey fox, dog, cat, various ground-squirrels (Pirote, Wyoming, Beechey's and Columbian), the chipmunk and the beaver, woodrat, white-footed mouse, meadow mouse and varieties (the Sawatch and Tule), musk-rat and Norwegian rat, the varying hare, the jack-rabbit, black-tailed jack-rabbit, cotton-tail rabbit, sheep and calves. The following birds also: Ruffed grouse, sharp-tailed grouse, sage hen, bobwhite quail, horned owl. In *Canada*: Richardson ground squirrel, Osgood's white-footed mouse, Drummond meadow mouse, varying hare and white-tailed jack-rabbit, Franklin's gull. In *Sweden*: The lemming, varying hare. In *Russia*: The dog, little ground squirrel, Steppe lemming, water rat, the introduced musk-rat, hamster, continental vole, large water vole, house mouse and long-tailed field mouse. In *Turkey*: The continental vole (*Microtus arvicola*), house and harvest mouse. In *Austria*, *Czechoslovakia* and *Poland*: Rabbit and hare. In *Tunisia*: The rabbit, and in *Japan* the local rabbit (*Lepus brachyurus*). Undoubtedly in America the most important reservoir of infection is the jack-rabbit and its congeners.

Man is extremely likely to contract the disease from animals, consequently laboratory infections are very frequent.

The nasal secretion and the urine of infected mice and rabbits are infective for other animals. Although *Br. tularensis* has been demonstrated in the sputum there is no evidence of its direct spread from man to man by this route.

Pathology.—In animals there is usually a fatal septicæmia. The pathological appearances of infected guinea-pigs and rabbits at autopsy much resemble those of plague in the same animals. In an experimentally-infected guinea-pig there is hæmorrhagic œdema at the site of inoculation,



Fig. 58. Tularemia. Section of liver of guinea-pig showing aggregation of *Brucella tularensis* in hepatic cells.
(After Prof. R. P. Strong.)

with blood-stained peritoneal exudate, and diffusely enlarged spleen, in which characteristic small necrotic foci can be found. Similar lesions may be detected in the liver; on microscopic section of these organs a dense infiltration with polymorphonuclear cells can be found, but the organisms can with difficulty be detected (Fig. 58). In the spleen of the mouse, on the other hand, little or no leucocytic response occurs; and when stained with Twort's light-green neutral-red stain, *Br. tularensis* can be readily demonstrated in large numbers. In the few recorded fatal cases in man nodules have been found in the lung and spleen.

Symptoms.—The incubation period appears to be from one to ten days. Unrecognized cases of tularemia are probably common in the endemic areas, for it may occur as a generalized disease without local lesions, or local lesions may be present with secondary lymphadenitis, which may not cause grave constitutional disturbances. As a rule, in the cases which have been so far recorded, a definite fever is present. The onset is sudden, with headache, backache, and fleeting pains, remarkable lassitude, and pyrexia which may last for three weeks or more; the extreme range of temperature is about 104° F. The pyrexia may subside to normal, or nearly so, from the third to the sixth day. The pains commence at some particular point and persist for two weeks to a month, though localized ones of greater or lesser degree may recur for the succeeding twelve months. Epistaxis and dizziness are common: weakness and lassitude persist for weeks after the pyrexia has subsided

and it may be months before normal health is restored. The spleen is not palpable. Typhoidal tularæmia has been observed in about 5 per cent. of cases.

Such is the description of the generalized disease as it is met in man. When infection results from inoculation, the effect may be purely local; an inflamed papule occurs at the site, with secondary lymphadenitis. After the bite of an infected chrysops, or other fly, on some exposed surface of the body, the onset is sudden, with pains and fever. The initial ulcer, which may develop within 48 hours, presents a process of diffuse necrosis with infiltration of the base. Sometimes subcutaneous nodules resembling sporotrichosis appear on the anterior and posterior aspects of the forearm and along the lymphatics between the ulcer and the regional glands. They are firm, movable, tender and 4-10 mm. in diameter. The patient may be prostrated and have to retire to bed; the lymph-glands draining the bitten area subsequently become inflamed and swollen and suppuration may occur. Subcuticular roseolar rashes on the body and arms are sometimes observed in Western America. Nodular and pustular lesions have also been recorded.

Three cases of laboratory infection of tularæmia have been recorded in England. Though the debilitating effect is very marked, only one death, in a series of seven cases reported from Utah, has been recorded, and this took place from apical pneumonia. There is, apparently, a lasting immunity in man. There is no record of a second generalized attack, though, as in Francis himself, a local re-infection may occur.

Infections of the eye and conjunctiva, causing acute conjunctivitis, were recorded by Vail, Lamb, and others. In America, an ocular-glandular process is well recognized. The primary lesion is of the conjunctiva and there is a regional lymphadenitis of the head and neck. Severe conjunctivitis results, with chemosis and œdema of the lids and surrounding tissues. There is now little doubt, as pointed out by Herrens-chwand (1935), that "Parinaud's conjunctivitis," first described in Paris in 1889, is none other than ocular-glandular tularæmia. Parinaud recognized that it was infectious and that it was associated in some manner with animals. It is characterized by the granular condition of the lids, with chemosis of the conjunctiva, inflammation and enlargement of the pre-auricular lymphatic glands.

Diagnosis.—This disease is most readily reproduced by inoculating material from the patient's ulcer, or gland-juice obtained by aspiration, into guinea-pigs, mice, or rabbits, thereby producing generalized tularæmia in these animals, from whose tissues the organism may be isolated on special media. The organisms are rarely present in the blood of human cases. Agglutination tests can readily be performed; the serum of patients suffering from the disease will agglutinate suspensions of the organism in high dilutions but, as pointed out by Ledingham, where cultures of *Br. tularensis* cannot be obtained, the spleens of infected mice contain the organisms in such large numbers that an emulsion in formalinized citrate solution may be used instead. Agglutination occurs in the second week, reaching its maximum between the fourth and eighth weeks, when there is a gradual fall, but it may persist for eleven years.

It has been ascertained that a cross-immunity frequently co-exists between tularæmia and the undulant fevers.¹ Calder stated, too, that tularæmia serum agglutinates *Proteus OX19* in a dilution of 1 : 80 and over in 13·5 per cent. of cases.

An intradermal test with a suspension of killed organisms has also been introduced.

The differential diagnosis of this condition has to be made from plague and from rat-bite fever. In both cases alike it depends upon the recognition of the respective specific organisms.

Treatment.—The patient should be kept in bed for several weeks after the subsidence of the fever. Convalescence should be prolonged. The inflamed glands should be dressed with a saturated aqueous solution of magnesium sulphate. Incision is inadvisable, unless suppuration is observed.

Streptomycin (see also p. 267) has a wide and intense potency in animals. In contrast to penicillin it has a maximal action on Gram-negative bacteria. Of all the infections of man in which streptomycin has been tried out it has the maximal effect in tularæmia. Intramuscular injections are given at intervals of three to four hours. The benefit is striking and 1 grm. daily for seven days will terminate the disease when of average severity. Out of 67 so treated there were 63 recoveries (*Report of Amer. Med. Ass.*, 1946).

Prophylaxis.—Prevention depends in part upon the avoidance of contact with infected rabbits in the endemic area. The dangers of experimental work with *Br. tularensis* in the laboratory have already been sufficiently emphasized. The prevention of the disease, from the public health point of view, is by no means easy. Sick or dead rabbits must be handled with great caution and rubber gloves must be worn by laboratory workers, marketmen, cooks, etc., in view of their great liability to infection. Cooking destroys the infection, as does also prolonged freezing.

¹ Confirming that *Pasteurella tularensis* is, in fact, *Brucella tularensis*.

CHAPTER XIV

MELIOIDOSIS

Synonyms. Stanton's Disease; Pneumo-enteritis; Pseudocholera.

Definition.—This is a rare, glanders-like disease occurring in Burma, the Malay States and Ceylon. A few isolated cases have been described elsewhere, including Europe, and three have been recognized in the United States. The name melioidosis was suggested by Stanton and Fletcher in order to describe its close relationship to glanders (*μῆλῐς*, used by Aristotle for a "distemper of asses" and *εἶδος* = form). Melioidosis has many resemblances to tularæmia, both are diseases of rodents accidentally attacking man.

Ætiology.—*Pfeifferella whitmori* (sometimes known as *Malleomyces pseudo-mallei*) closely resembles *Pf. mallei*; it is a small bacillus about the same size and shape, and occurs in very large numbers in all acute lesions of the disease. In films stained by Leishman's method, bipolar staining is very common. Acid-fast granules, decolourized by alcohol, were described by Mayer and Finlayson (1944). On culture also it resembles the glanders bacillus very closely, but is more actively motile and liquefies gelatin more rapidly. It grows luxuriantly upon peptone agar, forming a dense wrinkled culture, especially when the medium contains glycerin. A peculiar aromatic odour, reminiscent of truffles, is given off, though on repeated subcultures this feature is lost. On broth cultures a pellicle is formed. Brown, Duncan and Henry have shown that *Pf. whitmori* can be distinguished from *Pf. mallei* by its behaviour on a peptonized medium containing 1 per cent. sodium fumarate. This organism is pathogenic for most laboratory animals; for guinea-pigs, at any rate, the infection is more rapidly fatal than glanders, but in each case, in the male, acute orchitis is produced on intraperitoneal injection—the so-called Strauss reaction. Penicillin-treated plates are useful for isolation of the organism when other contaminants are present. There may be difficulties in distinguishing Whitmore's bacillus from achromogenic forms of *Ps. pyocyanea*.

Susceptible animals can be infected by scarification, by feeding or by simple application of cultures to the nasal mucosa; a characteristic feature in infected animals is discharge from the nose and eyes.

The organism is excreted in the urine and fæces of infected laboratory animals, while several cases of natural infection, especially in rats (*Mus griseiventer*, Bonhote), cats and dogs, have been observed. In 1927 the first case was reported in a horse from the Malay States, when the bacillus was isolated from nasal pus. *Pf. Whitmori* has been isolated from lung abscesses in sheep in Queensland.

Pathology.—The lesions vary very considerably. Numerous small pulmonary abscesses, roughly resembling those of miliary tuberculosis, are produced. Nodules which coalesce and break down into abscesses are found in the liver; they somewhat resemble those of portal pyæmia, and have to be distinguished from amebic abscesses. The organisms have been recovered from the blood, urine, sputum, and fluid from cutaneous vesicles of patients dying from the disease. In laboratory animals, artificially infected, small nodules form in the internal organs (Fig. 59).

Symptoms.—The accounts so far published of the symptomatology are meagre. The first cases observed by Stanton in 1917 were suffering from an acute diarrhœa,



Fig. 59.—Characteristic appearance of liver abscesses due to Melioidosis.
(Dr. A. T. Stanton)

with collapse roughly resembling that of cholera, and it appears that several patients who recovered from the initial intestinal attack died later from a form of septicæmia with pulmonary lesions resembling tuberculosis. During 1921 a few more cases were encountered, with similar symptoms. Only two are known to have recovered. There is usually a high remittent and somewhat irregular pyrexia. Delirium and mania appear to be frequent terminal symptoms. What appears to be a chronic form of the disease is also recognized; in this the lesions are found in the skin and subcutaneous tissues, leading to cutaneous abscesses and collections of pus in the liver, lungs, and spleen. The initial signs may be those of acute parotitis. Five cases occurred in West African soldiers in Burma during 1946 and have been studied by Harries and colleagues (1948). They ranged in severity from a fulminating disease to one of slow suppuration in localized abscesses. A peculiar case has been reported in England (1943) by Grant and Barwell in a soldier who had served in Malaya. A latent period of three years elapsed between possible infection with *Pf. whitmori* and the onset of clinical manifestations. The case was characterized by parotid swellings, abscesses, osteomyelitis of frontal bone, perispinal abscesses and bronchopneumonia. A second and almost identical case was diagnosed in a British soldier in South Africa in 1944. He had served in Singapore (Mayer and Finlayson) one year and eight months previously. This patient did not react positively to injection of 0.2 ml. of 1 : 10 dilution of mallein. An afebrile case with cervical adenitis, with ultimate recovery in an Indian artisan is reported by Green and

Mankikar (1949). Very few cases have been recognized in women, but in them the brunt of the disease falls upon the bladder and kidneys. The disease is said to be specially common in morphia addicts, but this is probably a coincidence. However, if man is infected, as a general rule, is still uncertain.

Diagnosis.—This is obviously best carried out by isolation of the bacillus from the faeces, urine, or blood, and differentiation from the glanders bacillus. In acute cases it may be isolated from the blood on the fifth day of the disease (Mirick) and has been obtained from the cerebrospinal fluid (Martin). Stanton and Fletcher found that the blood-serum agglutinated cultures of the organism in high dilution (1 in 2500 to 1 in 3000), a fact which is extremely useful in diagnosis; a titre of 1 : 80 is significant: 1 : 160 diagnostic. Differential diagnosis from malaria, typhoid, dysentery, tuberculosis, plague, cholera and even amoebic liver abscess, may have to be established. There are several resemblances to tularemia, and both are characterized by pyæmic nodules.

Serological procedures for diagnosis are agglutination, hæmagglutination, and complement-fixation tests. For the former formolized suspensions of a smooth strain are used and readings made after four hours' incubation at 37° C. or 18 hours on the bench. Agglutination is the O granular type. Hæmagglutination test is done with horse or human blood (group O, Rh-negative). The erythrocytes are tested with trichloroacetic acid extract of *Pf. whitmori*. Readings are made after one hour's incubation. Complement-fixation tests are also relied upon.

Differential diagnosis from glanders is more complicated. Patients infected with *Pf. whitmori* give a positive reaction to mallein, whilst horses infected with melioidosis give a negative test. Central chemotaxis and slight tendency to extension of the lesions, characters regarded by McFaydean as peculiar to glanders, are found in melioidosis.

Prognosis.—Most patients die within ten days of the onset; in chronic cases they may be ill for three to eight months or longer.

Treatment.—Harries (1948) and colleagues recommend sulphamethazine, 2 gm. four-hourly, as effective and safe. All accessible abscesses should be incised and treated locally with injections of penicillin. Autogenous vaccines cause active immunization where there is no rise in titre of agglutinins in the serum. Green and Mankikar (1948) have shown that chloromycetin exerts an inhibitory effect upon *Pf. whitmori*, suggesting that this antibiotic should be used in treatment.

CHAPTER XV

THE UNDULANT FEVERS (BRUCELLOSIS)

Preliminary statement.—Originally the term undulant fever was employed to designate a type of fever, commonly found in Malta and the Mediterranean area generally, which was usually referred to in medical literature as “Malta fever.” Experience, however, has shown that several closely allied fevers are to be classified under this heading. These fevers are due to infection by organisms of the genus *Brucella*. The following varieties of these organisms and their associated fevers are now recognized :

1. *Brucella melitensis* (formerly known as *Micrococcus melitensis*) which is originally a parasite of the goat and which is usually conveyed to man in goat's milk.

2. *Brucella abortus* (formerly known as *Bacillus abortus*, Bang) which is originally an infection of the cow, in which it causes abortion. A strain (*Brucella suis*) also occurs in the pig.¹ The infection appears to be conveyed to man through cow's milk.

I. UNDULANT FEVER (MELITENSIS TYPE)

Synonyms. Febris Undulans; Malta Fever; Mediterranean Fever; Gastric Remittent Fever.

Definition. A disease of low mortality, indefinite duration, and irregular course, undulant fever is the result of infection by a specific germ—*Brucella melitensis*. In its more typical form it is characterized by a series of febrile attacks, each individual one, after lasting one or more weeks, gradually subsiding into a period of absolute or relative apyrexia, also of uncertain duration. Common and characteristic complications are a rheumatic-like affection of joints, profuse diaphoresis, anæmia, liability to orchitis and neuralgia. Although only occasionally fatal, the disease is a fruitful source of inefficiency and invaliding.

History and geographical distribution.—Formerly confounded with typhoid and malaria, undulant fever has been established as a separate disease by the labours of various observers—Bruce (1887), Hughes, Gipps, Wright, Semple, and Bassett-Smith. Undulant fever appears to be more widely distributed than was formerly thought. It is not confined to Malta, or even to the Mediterranean; it may occur in Italy, France, Spain, the Red Sea littoral, India (Punjab), China, South Africa, Somaliland, West Africa, the West Indies, the Philippines, South America, Mexico and the United States, especially in New Mexico and Texas. Owing to the close relationship between *Br. melitensis* and *Br. abortus*, and the clinical resemblance between the two forms of fever they produce in man, it is extremely difficult to state the exact geographical range of each. It has been matter of great surprise that *Br. melitensis* has been discovered outside its hitherto known range. It has been proved to exist in the Pfalz region of the Rhineland in goats, sheep and also in a considerable number of persons who look after them. Wundt (1955) has reported that there has recently been a considerable spread of this fever in Germany.

¹ Another species of *Brucella* is found in pigs (*Br. bronchiseptica*)—but there is no reason to believe that it is communicable to man.

Epidemiology and endemiology.—The most susceptible age is between the sixth and the thirtieth year. Length of residence does not influence susceptibility. In Malta, the natives suffer as well as visitors, while there, and in other places where the disease is endemic, it occasionally assumes an epidemic character. The period of its greatest prevalence is the season of lowest rainfall, embracing June, July, August and September, the disease differing in this respect from typhoid which, in Malta, is more prevalent during the succeeding months, but a few cases may occur all the year round. This is explained, not only by the greater consumption of goats' milk during the summer months, but also by the fact that, following the birth of the kid in spring, contamination of the milk is more marked. The goats are not necessarily ill, except for their liability to abort. The disease tends to occur in particular towns or villages, in particular houses, barracks, hospitals, and rooms, and in particular ships, manifestly originating in limited foci of infection. Certain ships were formerly notorious foci of the disease. All classes were liable: the officer and his family as well as the soldier in barracks or the sailor on shipboard. The organism has been found in mothers' milk, so may presumably be transmitted to sucklings.

It is not correct to assume, as has so often been done, that because of these essential discoveries, undulant fever has been banished entirely. The cases amongst the British military and naval population dropped from 245 in 1905 to 12 in 1907 in Malta, but during the years 1929–35, there was a great increase in the number of cases among the civil population. Gatt (1938) reported that among the latter the incidence of the disease increased till 1934, when as many as 7·25 per mille were infected. Among the indigenous inhabitants there is a deep-rooted prejudice against boiling milk, and they are not content unless the goats are actually milked on their doorstep. However, tinned preserved milk is coming rapidly into favour among the poorer inhabitants as an infant food.

Undulant fever is not, generally speaking, transmitted directly from one person to another; that is to say, is not, as a rule, directly communicable from the sick to the healthy. The germ is readily conveyed by inoculation; the prick of a contaminated needle will suffice. Moreover, it is a well-recognized fact that undulant fever is the most easily acquired in the laboratory from handling cultures. An outbreak of 45 cases in a bacteriology class, of which one ended fatally, was reported by Huddleson and Munger (1940) in Ohio. In this case the actual method of infection could not be determined. Living emulsions of the micro-organism should never be handed round for class work; similarly, infection may be conveyed by sucking a thermometer recently used by a patient. A very striking circumstance is that in some hospitals the nurses and attendants in the fever wards are ten times more liable to the disease than people not so employed.

Milk.—Facts point very distinctly to goat's milk as the most important medium. The organism is present in the milk of 10–50 per cent. of Maltese goats, and monkeys were easily infected by feeding them on it. Directly the supply to the naval and military hospitals in Malta was stopped the cases of locally-acquired undulant fever practically ceased. Formerly this fever was very common in Gibraltar. The milk supply of the garrison at that time was largely from animals imported from Malta. Gradually

these goats have died out or been got rid of, and no more have been imported. Concurrently with this there has been a marked and proportional reduction of undulant fever cases in the garrison, so that, as a cause of disability, it has now quite disappeared from the records of the British Army and Navy. There is one well-authenticated instance of wholesale infection from this source in the s.s. *Joshua Nicholson*, which shipped 65 goats in Malta; an epidemic of undulant fever broke out on board, and nearly all those who drank the milk of the goats were attacked.

Cheese.—There is a considerable amount of evidence that undulant fever can be acquired by eating cheese made from the milk of infected goats. Several varieties of cream cheese made in the South of France, and even ripened cheeses such as Camembert, have fallen under suspicion.

Manure.—In the department of Aude near the Pyrenees, infection by handling manure soiled by urine of infected goats and sheep is regarded as possible.

Ætiology.—Bruce in 1887 demonstrated the presence in the spleen in undulant fever of a special bacterium—now called *Brucella melitensis*—and, by a series of experiments, proved that it was the cause of the disease. Unfortunately, as the bacterium occurs only sparsely in the general circulation (unless in the earlier stages, when the temperature is high), to search for it in the blood in the later stages does not aid diagnosis. The organism is present in abundance in the spleen pulp, and also in the lymphatic glands, in which it persists longer than elsewhere, and from both of which it can be recovered by cultivation. Bruce found it in the spleen in ten fatal cases. His results have been confirmed by many other observers. Injections of pure cultures give rise to a similar disease in monkeys and other animals, from whose blood the bacterium can be recovered, cultivated afresh, and injected into other animals, when it will again give rise to the disease. In five recorded instances, inoculation—intentional and accidental—of cultures of the bacterium into man has been followed by the characteristic symptoms after an incubation period of from five to fifteen days.

A variety of this organism, *Brucella paramelitensis*, which gives different serological reactions from those of the original strain, has been recognized as responsible for those cases of clinical undulant fever in Tunis and Algeria which do not give a high agglutination reaction with cultures of *Br. melitensis*.

Br. melitensis measures $0.33\ \mu$ in diameter. It occurs generally singly, often in pairs, sometimes in fours, but never, unless in culture, in longer chains. It is Gram-negative and readily stained by a watery solution of gentian-violet, and is best cultivated in a $1\frac{1}{2}$ per cent. very feebly alkaline peptonized beef agar; in this medium, some time after inoculation, it appears as minute, clear, pearly specks. After thirty-six hours the cultures become a transparent amber; later they are opaque. No liquefaction occurs in gelatin. The individual colonies are small, round, somewhat raised discs growing to 2–3 mm. in diameter about the ninth day. The optimum temperature for growth is 37°C . In bouillon it may produce a general turbidity. As a rule, the organism cannot be cultivated under anaërobic conditions. Recently, it has been discovered that the vitamin complex known as *biotin* is essential for its growth. No indol is formed, and the organism does not ferment glucose. Milk and other media are rendered alkaline.

At one time, *Br. melitensis* was believed to be a delicate organism, but investigations have shown that it can live for a long time in water, in dust, or on the

clothes of patients, and that it is not killed by cold or desiccation. Moreover, it is now known to be excreted in the urine of man in 10 per cent. of convalescent cases, and to occur in great abundance in the milk and urine of apparently healthy Maltese goats (50 per cent.), and probably of some cows. It has also been found in dogs (9 per cent.), sheep and horses. These facts account in part for the great frequency and dissemination of the disease in such insanitary places as Malta, to which place they specially refer.

Br. melitensis can be cultured from the blood-stream during the height of the fever in a considerable proportion of cases. A liver infusion—Staffseth's medium—is now commonly employed as selective culture medium. It has occasionally been obtained from the fæces. The serum of undulant fever cases of this and the *Br. abortus* type, as well as the milk of infected goats, will agglutinate it. The organism has been recovered from the gall-bladder by Eyre. Amongst the smaller laboratory animals the guinea-pig is highly susceptible to inoculation, a minute intraperitoneal dose causing prolonged infection.

Br. melitensis was stated by Evans, Myer, Shaw, and others to be morphologically, culturally, and serologically similar to *Br. abortus*. Three strains, *melitensis*, *paramelitensis*, and *abortus*, are separable one from another only by tests of agglutinin absorption. This criterion must be applied to infections in animals and in man in order to determine their ætiology. Cultures of *Br. abortus* are agglutinated in high dilutions of the serum of patients suffering from *melitensis* undulant fever.

It is well known that *Br. melitensis* may produce abortion in goats, though the animals themselves may exhibit no other clinical changes.

In monkeys intramuscular injection produces within three days a rise of temperature and death within three weeks. According to Burnet and Conseil, *melitensis* is at least a thousand times more pathogenic for these animals than is *abortus*. Indeed, only enormous doses of *abortus* will produce any effect at all in small monkeys.

Relationship with *Br. abortus*.—Intermediate strains of *melitensis* and *abortus* have in recent years been isolated from cow's milk, especially in England. In 1940 a strain of *Brucella* indistinguishable from *melitensis* was isolated from a farm in Staffordshire, and a further outbreak was reported in October, 1941. Subsequently, after an overall enquiry in twenty counties, another two outbreaks were discovered. In all cases it was found to be associated with true *Br. abortus* in the same herd.

Eventually it was recognized that organisms exist which, behaving under laboratory tests like *Br. melitensis*, have not all the features of this organism, especially in regard to pathogenicity. Out of 350 strains of *Brucella* isolated from milk by R. Cruickshank four were found to be antigenically *melitensis*, but, from the biochemical aspect, *abortus*. Strains from S. Italy have been found to behave like *abortus* antigenically and *melitensis* biochemically.

Pathology.—The disease has almost no pathological anatomy. The spleen is the only viscus which is distinctly diseased. This is enlarged (average 17 oz.), soft and diffuent; on microscopical examination the lymphoid cells are found to be increased. There may be some congestion and even ulceration of the intestinal mucosa, but this is not an essential feature. Other organs show chiefly cloudy swelling, and glomerular nephritis may be present.

Symptoms.—The period of *incubation* in the naturally-acquired disease is difficult to fix. Cases have occurred as early as six days after arrival, others as late as fourteen and seventeen days after leaving Malta. Some

hold that the disease may remain latent for months. It begins generally with lassitude and malaise, such as is associated with the incubation of many specific fevers, particularly typhoid. There are headache, bone-ache, anorexia, and so forth. Pain in the eyes, especially on lateral movement, is very characteristic. There may also be a peculiar sensitiveness of the alveolar margins of the jaw and painful movement of the temporo-mandibular joint. At first the patient may go about his work as usual. Gradually the daily task becomes increasingly irksome, and he takes to bed. Headache may now become intense, and, in addition, the patient suffers from thirst and constipation. At the outset the symptoms, except that there is very rarely diarrhoea, resemble those of typhoid, and epistaxis is not uncommon. There are no rose spots, however, then or at any subsequent period. There is evidence, in the coated tongue, which looks as if covered with white paint, in the congested pharynx, the anorexia, and the epigastric tenderness, of gastric catarrh; and the occasional cough and harsh, unsatisfactory breathing at the bases of the lungs indicate some degree of bronchitis or of pulmonary congestion. There may also be delirium at night, but as a rule there is insomnia. The fever is usually remittent, the temperature rising about midday (generally about 2 p.m.), falling during the night, and the patient becoming bathed in a profuse perspiration towards morning. The spleen and the liver, but especially the former, are somewhat enlarged and, perhaps, tender. Lumbar pain may be severe.

After a week or two of this type of fever, specially distinguished by pains and perspirations, the tongue begins to clean and the appetite to revive; but, notwithstanding these signs of amendment, the patient still remains listless and liable to headache and constipation. He continues feverish and at times perspires profusely. Gradually, however, although he is anæmic and weak, subjective symptoms become less urgent; he then sleeps well, he has no delirium at night, and can take food, although the body-temperature may still range slightly above the normal. Then once more, and perhaps over and over again, fever with all the former symptoms gradually returns; and now, if it has not

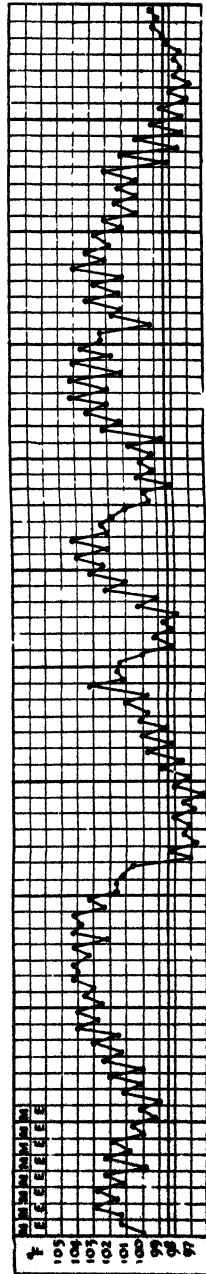


Chart 14.—Undulant fever : typical case. (By permission of London School of Hyg. and Trop. Med.)

declared itself before, the peculiar fleeting rheumatic-like affection of the joints or fasciæ, so characteristic of the disease, shows itself in a large proportion of cases. One day a knee is hot, swollen, and tender; next day this joint may be well, but another is affected; and so this metastatic, rheumatic-like condition may go on until nearly all the joints of the body have been involved one after the other. Effusions have been reported from which *Brucella* has been cultured. Purulent synovitis of the costosternal and costochondral joints sometimes occurs. Arthritis and osteitis of the foot with bone atrophy and blurred contours of the joints between the cuneiform and metatarsal bones have been described by Weil. The patient may suffer also from neuralgia in different nerves—intercostal, sciatic, and so on. Orchitis is an occasional early complication, and may be mistaken for testicular mumps. In some cases these complications are severe and characteristic; in others they may be mild, or absent altogether. In this respect the same infinite variety exists as in other specific fevers. In severe cases a purpuric condition with bleeding from the gums is occasionally observed. General enlargement of the lymph glands has recently been described.

The most characteristic feature of undulant fever is the peculiar behaviour of the temperature (Chart 14). In a mild case there may be a gradual ladder-like rise through a week or ten days to 103° or 104° F., and then through another week or so a gradual ladder-like fall to normal, the fever, which is of a continued or slightly remittent type, disappearing for good without complication of any sort in about three weeks. Such mild cases are the exception. Usually, after a few days of apyrexia, absolute or relative, the fever wakes up again and runs a similar course, the relapse being in its turn followed by an interval of apyrexia, which is again followed by another relapse; and so on during several months. This is the "undulant" type from which Hughes derived the name he suggested for the disease—*febris undulans*. A factor of practical importance from the diagnostic point of view is the tendency for the fastigium of the temperature curve to occur towards midday or early afternoon; this feature distinguishes it from typhoid, in which the maximum rise generally occurs towards 6 p.m., or from other long-continued septic fevers, such as that in hepatic abscess, in which this takes place towards night-time.

In cases of another class a continued fever persists for one, two, or more months, with or without the usual rheumatic, sudoral, and other concomitants—the "continued" type of Hughes.

Usually remittent or nearly continued in type, in a proportion of instances (generally *paramelitensis* infections), the fever exhibits distinct daily intermissions, the swinging temperature chart suggesting sepsis, endocarditis, or malaria. This is the "intermittent" type of Hughes (Chart 15).

In some patients, two to three months may elapse before they are finally rid of the tendency to febrile attacks and characteristic pains and aches. According to Bassett-Smith, the average duration of the disease is four months, but it may last two years. The shortest period is about three weeks.

As in other bacterial diseases, cases of all degrees of severity are met. Bassett-Smith recognized five types:

(a) *Ambulant*.—The patients have no symptoms, but are excreting *Br. melitensis* in their urine and are naturally potential sources of infection. Afebrile cases occur with pleurisy and intercostal neuralgia.

(b) *Mild cases*.—These last about a fortnight and are apt to be mistaken for paratyphoid.

(c) The *ordinary type*.

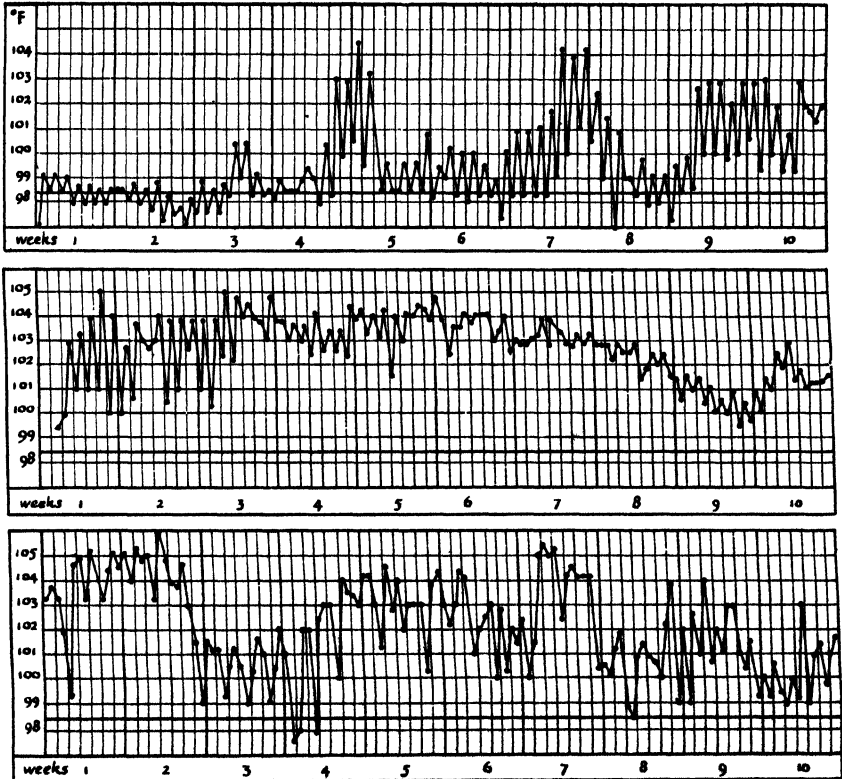


Chart 15.—Various types of temperature chart in undulant fever.

- (1) Intermittent type
- (2) remittent type
- (3) irregular type

(d) The *malignant type*, with hyperpyrexia and toxæmia. This may be fatal, and considerable difficulty may be experienced in making a diagnosis, as in the case reported by Archibald in which death took place on the twenty-seventh day.

(e) An *intermittent type* with hectic fever, sweats, and general wasting. This is apt to be mistaken for tuberculosis, and appears to be common in South Africa (Chart 15).

(f) A *chronic type* has been described with symptoms relating to the central nervous system with headache and nuchal rigidity. In such cases the spinal fluid may exhibit increased pressure.

As a rule, there is a moderate leucopenia (about 6,000 per c. mm.) with an increase of lymphocytes. Sometimes also a slight secondary anæmia is observed.

Surgical Brucellosis.—Hydrarthrosis of a single joint cavity and superficial abscess formation on the chest or abdomen, without generalized fever, may also be produced by *Br. melitensis*. Cases with arthritis of the hip joint have been described. Spondylitis of the mid-dorsal vertebrae has been recorded by Löffler and Moroni, and also in S. Italy by Molinelli and colleagues; but only in chronic infections. The Editor has seen one such case from Somaliland where, had not the organism been isolated from pus from a skin abscess, this possibility could never have been suspected. Chronic infection resulting in osteomyelitis of the long bones has been recorded.

Complications and sequelæ.—As a rule, by far the most serious consequences of undulant fever are the debility, the emaciation, the profound anæmia, the rheumatic-like pains, the neuralgias, and such sequelæ as abscess, orchitis, mastitis, parotitis and boils. Spondylitis of spine may ensue with parrot-beak proliferation of lumbar vertebrae (Spink, 1956). In the male, intermittent hæmorrhages from the urethra are not uncommon. Orchitis is estimated to occur in 4 per cent. of cases. Dixon and Roaf have recorded acute transient attacks of aphasia and, during convalescence, deafness and tinnitus. In women the disease is apt to give rise to ovarian pains, dysmenorrhœa, amenorrhœa and menorrhagia, and to favour abortion and premature labour. The germ may pass into the foetus; children born in such circumstances are weakly.

Complications, such as splenic and hepatic enlargement, enlargement of the mesenteric and cervical glands, suppuration, phlebitis, chorea, various psychoses, arteritis, endocarditis, pericardial effusion and melæna are met occasionally during the long course of the disease. When death occurs it is usually from suddenly developed hyperpyrexia; occasionally it is brought about by exhaustion, by hæmorrhages and purpuric conditions, or by some pulmonary complication such as pneumonia. Fatal gastric and intestinal hæmorrhages have been described on many occasions. In a few instances the fever is a fulminating type, rapidly ending in death from hyperpyrexia.

Neurobrucellosis.—Attention has been drawn to nerve complications (1951); these may occur as a complication during the course of the fever, during convalescence, or long after apparent recovery. It may produce symptoms of meningitis, encephalitis, myelitis, radiculitis, peripheral neuritis, paræsthesia, and facial neuralgia.

A comparatively common sequel is chronic inflammation of the sacro-iliac joint. The organism has been recovered from the brain and C.S.F.

Diagnosis.—The diagnosis of undulant fever from typhoid is an important practical matter and may be difficult in the early stages. Reliance has to be placed principally on the characteristic temperature

curve, the presence or absence of rose spots, of diarrhoea, of joint complications, and of sweats, the locality where and the season in which the disease was contracted, and the agglutination test. There may be considerable hesitancy in differentiating it from pulmonary tuberculosis, especially in the intermittent form, and there are cases of undulant fever with pulmonary signs and symptoms which may resemble that disease. Undulant fever, moreover, may "light up" a quiescent tuberculosis.

An *intradermal* or "melitene" reaction (Burnet, 1922) is 0.2 ml. of a killed broth-culture, containing half a million organisms, is injected into the skin. If the reaction is positive, a red oedematous area results at the site and persists for several days. Adequate controls with broth and cultures of other organisms should be performed in adjacent areas of skin. The melitene¹ reaction is best performed by injecting 1/10-1/20 ml. of the filtrate of a 20 days' broth culture into the skin 4 in. above the elbow. In typical cases the reaction, which consists of a red plaque 4-6 cm. in diameter, becomes positive in six hours and persist for two days. The reaction is positive on the seventh to tenth day of the fever and persists for ten months after recovery. It has been asserted by Wilson and others that, if this reaction is repeated, abscess formation may result; even gangrene of the skin has been observed.

Hæmoculture.—As early as the second day of the disease the organism may be recovered from the blood-stream. For this purpose 5-10 ml. of blood should be drawn off by means of an aseptic syringe and with great precaution distributed into several flasks of broth. The broth should be incubated at least twenty-four hours, or, if necessary, for as long as 26 days, and subcultures made from time to time on trypticin-agar slopes. On the fifth day, on further incubation, minute dewdrop-like colonies should become apparent, and the emulsion should be tested against a specially prepared immune serum in dilutions from 1 in 40 to 1 in 400. It is said that cultures from the blood-clot may sometimes give better results than those from the whole blood. The technique is described by West and Borman (1945). After removal of serum the clot is macerated and transferred to crystal violet tryptose broth in a screw-capped vial. The medium is adjusted to pH 6.9. The composition of this medium is: Bacto-tryptose 20 grm., bacto-dextrose 1 grm., sodium chloride 5 grm., para-amino-benzoic acid 0.1 grm., crystal violet (0.1 per cent. aqueous solution) 1.4 ml., distilled water 1,000 ml. The cap of the vial should not be tightened. Inoculate at 35° C. under CO₂ tension for 4-7 days. The culture is then streaked on to a solid medium consisting of bacto-tryptose agar containing 1 ml. per litre of 0.1 per cent. aqueous crystal violet. The inoculations are made once each week for three weeks and plates are incubated four days. The suspicious colonies are isolated and preliminary examinations made by slide agglutination tests. By this method cultures have been obtained in specimens which were negative to agglutination tests. The organism may be obtained by splenic puncture, though this method is rarely justifiable.

Isolation from the urine.—This is much more difficult to obtain than from the blood. The urine must be obtained either by catheter or midstream specimen after the fifteenth day of the disease. Every precaution must be taken to prevent contamination, to which *Br. melitensis* is very sensitive.

Agglutination test.—Agglutination, if performed by the macroscopic method and with modern technique, will generally give positive results. There are several important points to remember in connection with this reaction.

¹ The commercial preparation is known as "brucellergen."

A positive reaction may merely indicate sensitization, not necessarily active infection, as for instance, from milk containing antibodies.

Strain of organism employed for agglutination.—The serum, as a rule, contains no agglutinins until after the second week of the disease. It may be necessary to employ several strains of *Br. melitensis*, as well as cultures of *Br. paramelitensis*. Titres of agglutination as high as 1 in 6000 have been reported. A rising titre of agglutination is more significant, from the diagnostic angle, than the absolute titre.

As other sera are known to agglutinate the organism in low dilutions, it is recommended that the blood be heated to 56° C. for half an hour before being used for the test, in order to destroy non-specific agglutinins. The occurrence of a pro-agglutinoid zone (or zone of no reaction) may be a source of error, but only in higher dilutions, and it is possibly due to the presence of anti-agglutinins. It is necessary, therefore, to employ a considerable number of dilutions.

The serum of tularæmia agglutinates *Br. melitensis*. A problem of differential diagnosis may arise when a serum agglutinates both *Br. tularænsis* and *Br. melitensis* in equal titre. This can only be settled from a serological aspect by testing for the absorption of agglutinins.

Complement-fixation test.—No distinct advantage has been reported for this method over the agglutination test. It is, moreover, more complicated. Often the serum is found to be anti-complementary.

After the fever has gone on for several weeks, diagnosis is, of course, easier; in the early stages, on clinical grounds alone and, apart from the agglutination test, it may be, as already stated, almost impossible. Tuberculosis, abscess, empyema, malaria, relapsing fever, acute rheumatism, and all the causes of continued high temperature of a septic type have to be carefully excluded in attempting a diagnosis. The possibility of the concurrence of another infection—typhoid, for example—must not be overlooked.

Prognosis.—As a general rule, in military and naval forces the mortality-rate is low, from 2 to 6 per cent., but in the civilian population it may be considerably higher. Death may occur from hyperpyrexia, heart-failure, or pulmonary complications. Bassett-Smith pointed out that a persistent temperature of 104° F. may indicate a grave prognosis, as may also an intermittent pulse. Alarming symptoms may develop at any stage of the disease, especially in relapses. Though it may be unwise to forecast how long a fever may last, yet, when the pyrexia has subsided for more than ten days, and the patient's tongue is clean and his appetite good, no further relapses may be expected; but there is frequently a short terminal rise of temperature.

In the malignant type the death-rate may be 10 per cent. or more. Pneumonic complications are frequent and should be treated seriously. The after-effects of the disease are often incapacitating, especially the production of neurasthenia, neuralgia and cardiac weakness. The debility makes the convalescent an easy prey for any intercurrent disease. It is normally considered that, as a general rule, a lasting immunity is conferred by one attack.

Treatment.—*Aureomycin and other antibiotics.*—Daily doses of 60 mgm. aureomycin per kg. are well tolerated by man and 8 mgm. per kg. parenterally or intramuscularly.

Debono in Malta (1949) stated as his opinion that aureomycin cured this fever rapidly within one week. At first in 14 cases the treatment lasted eight days and the average total dose of aureomycin was 16 gm., but a relapse took place in 4, after a period as long as seven weeks on 2 gm. daily. Sudden and well-marked elevation of temperature termed "spiking" at the beginning of the treatment was noted in all. He recommended, that in order to effect a final cure, treatment must be extended over a period of twelve to fourteen days at 2 gm. daily—one capsule every three hours. No serious reactions have been reported.

The biggest series has been reported by Killough and colleagues (1951) in 39 patients in Egypt. Twelve were treated with chloromycetin (chloramphenicol) in daily doses of 50 mgm. per kg. for a period of twelve days. The total amount was 36 gm. They became afebrile in an average period of 5.1 days. Eleven were given aureomycin in daily and total doses of the same amount, or 50 mgm. per kg. for twelve days. The use of BAL (see p. 868) in conjunction with aureomycin and chloromycetin has been recommended by Renoux and Roux in animals, especially guinea-pigs, and it is suggested that this procedure might be found advantageous in human cases refractory to these antibiotics. *Terramycin* has been given to 16 patients, in daily doses of 7.5 mgm. per kg. and a total dose of 44 gm. over a period of 11 days. They became afebrile in an average of 3.4 days. Relapses were comparatively common. No serious toxic effects were noted, but it is clear that terramycin is as good as the other antibiotics in producing excellent clinical response.

Cathomycin, or *Novobiocin* (see p. 876) a new antibiotic, introduced for organisms resistant to penicillin, is claimed by Gost (1958) to be specific for this type of undulant fever in Spain. There were 26 cases all of which were cured and there were no recurrences. Out of these 20 were positive by blood culture. The temperature remained unchanged for the first five days of treatment. On the fifth day the fever was resolved by crisis when all symptoms disappeared with reduction of splenomegaly. The dose for adults of the drug in capsule form is 0.25 gm. four hourly until the day after the crisis. Then it is given six-hourly till a total of 18 gm. Urticarial rashes were apt to ensue on the eighth day of treatment.

The diet at first should consist of milk (in Malta, boiled); later, of broths and eggs and, if necessary, stimulants; but it should be noted that on sulphonamide treatment stimulants should be omitted. Solids must not be freely given during high fever or when the tongue is coated. If appetite is present, ordinary simple food may be taken. Lemonade or lime-juice should be given after a time; not merely as a pleasant, thirst-relieving beverage, but with a view to averting scurvy if the dietary be too restricted over a long period. Feeding must be conducted with the greatest circumspection, avoiding overfeeding on the one hand and a low monotonous diet on the other. The tongue and the appetite are the best guides.

Prophylaxis.—Wherever this fever is prevalent resorts should be avoided by pleasure- and health-seekers during the summer. As a matter of precaution, in the endemic areas, the drinking-water and food ought at all seasons to receive special attention. *All milk should be avoided, or sterilized by boiling*, and food dishes should be washed with boiled water. Laboratory workers must be careful in handling cultures of the bacterium, for the accidental introduction of the organism into the conjunctival sac has sufficed to cause the disease.

The discovery that goat's milk is the principal medium through which undulant fever is communicated to man has led to very striking and important results. Unfermented cheese is a frequent source of infection and should be forbidden. In Toulon the disease has been traced to "fromage cervelle" made from the milk of sheep and goats.

These facts suffice to indicate the direction preventive measures should take. Infected goats may appear to be in perfect health and may milk satisfactorily.

The prevalence of infected animals is best determined by cultivating the organism from their blood or milk; failing this, serum reactions (p. 293) and Zammit's test are employed. The latter, which is known as the *lacto-reaction*, consists in diluting the milk to 1 in 20 and mixing it with a dense emulsion of *Br. melitensis* or *Br. paramelitensis*. The mixture is drawn up into the capillary tube and placed in the incubator for twenty-four hours, when any sedimentation present may be detected. It is better to heat the milk first to 56° C. for half an hour.

Zammit and Debono attempted to immunize the Maltese goat by dermal immunization. A filtrate of a broth culture, containing brucella organisms, is sprayed over the mammary region, into the mouth, and 1 ml. is injected intradermally in four places. The treatment is repeated four times on alternate days.

Prophylactic inoculation.—Nicolle and Conseil conducted some experiments on man which seem to show that it is possible to immunize against undulant fever by subcutaneous injections of killed cultures of the organism, and similar results were obtained by giving 100,000,000 organisms by the mouth on three consecutive days, and again on the fifteenth day. These results were controlled by subsequently injecting cultures of living organisms; the controls in both cases developed undulant fever.

Dubois and Sollier have employed a vaccine of various strains of *melitensis* mixed with two strains of *abortus*. The complete vaccine made up of five strains contains 2,000,000,000 organisms per ml. The first dose is 0.25 ml. or 500,000,000; the second 0.75 ml. or 1,500,000,000; the third 1 ml. or 2,000,000,000. The full course of injections was given to 111 persons engaged in dealing with infected animals, and none of these developed undulant fever.

II. UNDULANT FEVER (ABORTUS TYPE)

Synonym. Abortus Fever.

Definition.—A definite variety of undulant fever in man produced by *Brucella abortus*, the organism of contagious abortion of cattle and swine.

Geographical distribution.—Undulant fever of the *abortus* type in man has now been reported from the following countries: Italy, Canada, U.S.A., Denmark, Sweden, Germany, Holland, Switzerland, Austria, Poland, Palestine, South Africa, Rhodesia, New Zealand and Australia. In England the number of cases identified as *abortus* fever was growing yearly, and in 1933 over 140 were recognized and reported. Previous to this, sporadic cases had been reported from time to time and an attempt had been made to ascribe them to occasional drinking of goat's milk.

During the last twenty years there has been a remarkable reduction in this fever in Great Britain, mainly due to preventive measures undertaken.

Differentiation of *Brucella abortus* from *Brucella melitensis*.—*Br. abortus* is usually somewhat larger than *Br. melitensis*, being from $0.4\ \mu$ to $0.6\ \mu$ in thickness, and varying in length from $0.8\ \mu$ to 2.5 or even $3\ \mu$. The organism is remarkably pleomorphic; involution forms are unusual. *Br. abortus* can be isolated from the milk and uterine discharges of infected animals. Normal strains of *Br. abortus* of bovine origin cannot be grown in primary culture at the ordinary carbon-dioxide tension of the air, but to ensure growth it is necessary to raise the proportion of this gas to 5 per cent. or 10 per cent. by volume. These requirements diminish as the strain is propagated on artificial media. The simplest method of growing this organism is in a Bullock's jar in which cultures have been placed for incubation, adding a sufficient amount of pure carbon dioxide to produce the optimum concentration. In primary growth the colonies develop after inoculation in a zone 10–20 mm. below the medium. This behaviour is taken as evidence that *Br. abortus* is micro-aërophilic. After continuous subculture the organism can be grown under ordinary conditions. The porcine type, *Br. suis*, does not show the carbon dioxide growth requirements of the bovine type.

The organism grows best on glucose agar in which 2 per cent. glucose is added to a simple meat-extract agar medium set to reaction of pH 7.4, or in Fildes' medium. On potato slopes of alkaline reaction, differences in the growth character of *Br. abortus* and other organisms of the group may be found in week-old cultures; the former gives a uniform creamy-yellow growth, while *Br. melitensis* and *Br. paramelitensis* yield a greyish-chocolate or even black growth.

The reaction to dyes is important. The bovine *abortus* type is inhibited by the presence of thionin in suitable concentration, the porcine type by the presence of basic fuchsin, methyl violet, or pyronin. The *melitensis* type grows in the presence of all four dyes.

The formation of hydrogen sulphide from proteins or aminobodies containing sulphur is one of the most important biochemical reactions. The organism is grown on Staffsseth's liver-infusion agar medium at a reaction of pH 6.6 and, after sowing, a strip of lead-acetate paper is introduced into the tube. After forty-eight hours' incubation a distinct blackening of lead acetate occurs in tubes sown with *Br. abortus*, while *Br. melitensis* produces no H_2S at all. On serological grounds, by means of the absorption of agglutinin method, the bovine and porcine *abortus* may be differentiated from the *melitensis* type.

Pathology.—This is the same as in *Br. melitensis* fever. Occasionally, abscess of the spleen is observed. There is a general reticulo-endothelial hyperplasia of the lymph glands. Meningo-encephalitis with greyish-white tuberculations is reported in *Br. suis* infections in America.

ABORTUS INFECTION IN MAN

Diagnosis.—The agglutination test in *abortus* infections is much the same as in *melitensis*. An agglutination of 1 in 10 to 1 in 80, in the absence

of clinical symptoms, indicates a past infection, while a titre of 1 in 100 or over, in the absence of clinical symptoms, probably indicates a latent infection; a titre of 1 in 100, or over, in the presence of pyrexia and other symptoms of disease, may be considered as diagnostic of active infection with *Br. abortus*.

The agglutination test is best performed by the macroscopic method. A practical method of making a diagnosis by the agglutination test is by means of the "glutoscope," an apparatus devised by Bevan on the same lines as the abortoscope.

The intradermal test, or "abortin" reaction, is as useful in the diagnosis of *abortus* infection in man as is the parallel test in *melitensis*, and performed in the same manner (see p. 293).

Diagnosis by blood-culture is the same as for *Br. melitensis*, and is successful in about 16 per cent. of cases; (see p. 293). A certain amount of assistance may be obtained from the leucocyte count. There is usually a slight leucopenia with a relative increase in the lymphocytes. The average in seven cases of *abortus* infection under the Editor's care was leucocytes 6,800, with polymorphonuclears 43 per cent. and lymphocytes 48 per cent.

Symptoms.—On the whole, *abortus* infections run a much shorter course than those of *melitensis*. Some cases may be so mild that no obvious clinical signs are produced beyond the characteristic pyrexia. Atypical cases show slight fever, headache, listlessness, sometimes abdominal pain, sore throat and nocturnal sweating. As a general rule, however, prolonged pyrexial cases lasting many months, as in *melitensis* fever, are not common. On the other hand, *abortus* infections may be remarkably persistent over a year or more, but continued fever of over three months' duration is rare, though cases with multiple rigors and the characteristic undulating febrile curves have been recorded. Some of the most severe clinical cases seen in England have been the result of infections contracted in the laboratory.

Treatment.—Antibiotics, especially aureomycin, have been used to control the fever. In resistant cases the modern practice is to ring the change, so that if aureomycin and tetracycline fail when given singly, they should be given in combination and then switched over to terramycin or to achromycin.

CHAPTER XVI

ENTERIC FEVERS (AND BACTERIUM COLI INFECTIONS)

THE enteric group of fevers includes typhoid fever, due to *Salmonella typhi*, and paratyphoid fevers, due mainly to *Salmonella paratyphi-A* and *S. paratyphi-B*. Paratyphoid-C fever has a somewhat different symptomatology (see p. 805). These organisms belong to what is now known as the *Salmonella* group, and the fevers caused by them were classified during the 1914-1918 war as "enterica."

Prevalence.—Enteric fever is prevalent among young soldiers and recently-arrived civilians in the East, but, fortunately, liability to infection decreases with length of residence, owing apparently to acquired immunity. The well-known immunity of native races to typhoid is probably due either to mild attacks of the disease in childhood or to the immunizing effect of living in constant contact with typhoid infection. In insanitary native cities—Chinese, for example—where the European would almost surely contract typhoid, the natives have acquired a high degree of immunity. The typhoid and paratyphoid infections among Europeans in the tropics appear to be more virulent, and to cause a death-rate twice as heavy as that commonly observed in England. According to English statistics, the death-rate is given as about 1 in 8 attacked, but in India the death-rate was stated to be rather over 1 in 3.

Up to the early days of this century, typhoid in India used to kill more European soldiers than did cholera. Enteric fevers are apt to occur in camps in localities previously unoccupied by man. This has long been noted in India, while in Australia typhoid has occurred in the back country many hundreds of miles from human habitations. Enteric infections have been found frequent in Polynesia, especially in Fiji.

Epidemiology and endemiology.—The essential factor in the propagation of enteric fevers in the tropics, as in temperate climates, is the individual who is passing enteric bacilli in his urine or faeces, or in both. He may be in the acute or the convalescent stage, or a "carrier." Three kinds of enteric carriers are mentioned by writers on this subject: (a) The *acute carrier*, who passes enteric bacilli in the excreta for a short period after an attack of enteric fever. (b) The *chronic carrier*, who continues to pass enteric bacilli in the excreta for years, possibly permanently. Chronic carriers are more often women than men. The gall-bladder being the seat of a chronic infection, the carrier may be the victim of gall-stones and cholecystitis. (c) The *passive carrier* is one who continues to pass enteric bacilli in the faeces without having actually suffered from enteric fever.

The enteric carrier is a danger to the community, the degree of danger depending to some extent on his personal hygiene, but much more on the sanitary condition of the locality. Under an efficient water-carriage system of sewage disposal there is a minimum risk. Where the conservancy system—i.e., the dry closet—is employed, as in the tropics generally, the risk of infection is great. The modes of infection are: (1) directly from the infected person (patient or carrier) to the susceptible; (2) indirectly through water supply; and (3) indirectly by fly-carriage and contamination of food.

S. typhi is practically world-wide. Paratyphoid-A fever is the most common

form in the East (India), paratyphoid-B fever in Europe. During the 1914-1918 war the majority of enteric infections in France were paratyphoid-B, and the most extensive epidemic in the British and French troops was on the Gallipoli peninsula, in 1915. But, relatively to former campaigns, cases of typhoid were few, the armies being almost completely protected by antityphoid inoculation. In the earlier part paratyphoid-B was the prevailing infection, while in the later phases the cases were almost exclusively paratyphoid-A. Paratyphoid-C fever, which resembles the fevers caused by *S. ærtrycke* and *S. suispestifer*, is widespread in British Guiana, but elsewhere has probably not the epidemiological importance of the other three (Giglioli).

Ætiology.—*Description of organisms.*—*Salmonella typhi* is a Gram-negative motile rod, 2-4 μ in length and 0.5 μ in thickness. It is provided with numerous peritrichous flagella, and is very active when grown on artificial media. On these it thrives well, with growth resembling that of *Bacterium (Escherichia) coli*, but less dense. In its biochemical reactions it differs considerably from that organism, and produces acid without gas-formation in maltose, glucose, and mannite, but causes no change in lactose, saccharose, and dulcitol. It produces slight acidity in milk without clotting. No indol is produced in peptone water (see Table VII, p. 447). A method of identifying strains of *S. typhi* has been introduced by the discovery by Craigie and Yen of the type-specific typhoid Vi bacteriophages. By this technique it is possible to divide typhoid bacilli into a number of well-defined types. The phage type of a strain is a permanent character and the typing of the typhoid bacterium by these means gives reliable results. The paratyphoid bacilli A, B, and C resemble in their general morphological characters and staining reactions *S. typhi*, but differ from it in their biochemical and immunity reactions. They also, like *S. typhi*, are non-lactose-fermenters, but produce acid and gas in glucose, mannite, maltose, and dulcitol, though they do not affect saccharose nor form indol in peptone water. Paratyphoid-A bacterium is weaker in fermentative power than B, and it produces permanent acidity in litmus milk, whilst B first produces acid, returning later to a permanent alkaline reaction. Their immunity reactions are also quite specific. Paratyphoid-C bacillus (*S. paratyphi-C*) differs from B in its immunity reactions, and some bacteriologists might prefer to regard it as a serological race of *S. suispestifer*.

The portal of entry of the enteric bacilli into the tissues of their host appears to be the lymphoid masses forming the Peyer's patches and solitary follicles of the ileum. Here they cause a hyperplasia of the lymphoid tissues, followed at a later stage, in severe cases, by necrosis, sloughing and ulceration. The bacilli pass on to the lymphatic glands of the mesentery and posterior abdomen, which become enlarged. Finally, they enter the blood-stream. The period of bacillæmia coincides with the early febrile stage of the disease, and hæmoculture is successful in the majority of cases in which it is undertaken sufficiently early—i.e. while the temperature is still rising, or when it is continued without marked remissions. It is seldom successful after the first marked morning remission, especially in paratyphoid fever, or after lysis has commenced. The duration of bacillæmia varies greatly, depending on the severity of the case and duration of the pyrexia. It is, on an average, longer in typhoid than in the paratyphoid fevers. It is important, therefore, in the diagnosis of enteric fever, to set about hæmoculture as early as possible; every day's delay diminishes the chance of success.

Alternately, it has been suggested that in enteric infections the invading organisms enter the blood-stream first (possibly through the tonsils), and that the intestinal lesions are secondary to the bacillæmia.

Although bacilli are eliminated in the faeces and urine, they cannot always be

isolated from the excreta, even on repeated examinations, though the modern use of selective media has increased the proportion of successful results.

Bacteriophage typing.—This method of typing was introduced by Craigie and Branden in 1936. Those *Salmonellæ* which are susceptible to the action of bacteriophage are closely related to the type of O antigen present. Soon after the discovery by Felix and Pitt (1934) of the Vi antigen of *Salm. typhi*, several workers established the existence of bacteriophages acting specifically on bacilli containing this antigen.

Anti-Vi-phage was grown on typhoid strains of different origin, and the races of bacteriophage so obtained were found to have developed a high degree of specificity for that one particular strain in which they had been propagated. The evidence obtained from a study of the origin of the strains revealed a high degree of correlation between the bacteriophage type and the epidemic sources. The degree of specificity seems to be almost complete and the results are more constant and reliable than those obtained by typing by the fermentative methods hitherto in vogue. Only those species of *Salmonella* containing Vi antigen can be typed. Vi antigen is contained in *Salm. typhi* and *Salm. paratyphi C.*, but no less than 29 Vi-phage types are recognized. Other members, such as *Salm. paratyphi A* and *B* and *Salm. typhi-murium* contain Vi antigen specifically susceptible to bacteriophagy.

Pathology.—The most striking lesions found *post mortem* (in addition to the tissue changes common to all continued fevers) are: ulceration of the intestine, especially the Peyer's patches and solitary follicles in the ileum and jejunum; enlargement and congestion of the abdominal lymphatics; and enlargement and congestion of the spleen.

The most notable differences in the post-mortem appearances between typhoid and the paratyphoid fevers are: in paratyphoid fevers the intestines more frequently show no change, though they may be acutely inflamed throughout their length, the lymphatic tissue escaping; and in paratyphoid fevers ulceration of the *large* intestine is relatively more frequent. Paratyphoid-C is in many instances a septicæmia, and deep metastatic abscesses due to this organism are described by Giglioli.

Post-mortem bacteriology.—The causative organism in enteric fevers may be recovered *post mortem* from the intestinal lesions, enlarged abdominal lymphatics, the spleen, the gall-bladder, the heart's blood, and other tissues.

Symptoms.—The usual *incubation period* for all the enteric infections is about fourteen days, but it may be shorter than seven or longer than twenty-one days.

There is a wide range in the severity of the infections, and one clinical description cannot apply equally to all cases, from the mildest to the most severe. The variation is, however, more in the degree than in the nature of the clinical manifestations. After all that has been written, especially during the 1914-1918 war, on "atypical" enteric fever, this group remains, whether in inoculated or uninoculated patients, remarkably true to one type—which may be termed the "enteric type."

The typical *onset* is a gradual one, but it may, especially in paratyphoid fever, be sudden, with a shiver or even a rigor. Headache is the most constant early symptom, and is usually accompanied by malaise, anorexia, pains throughout the body and limbs, and insomnia. The tongue is coated, the mouth dry and uncomfortable, and the patient thirsty. There is a characteristic moist facies with cheek-flush, and general apathy. These symptoms vary greatly, and in the mildest cases may pass undetected. Epistaxis is more common in typhoid than in paratyphoid. There may be pain or general uneasiness in the abdomen, but in mild paratyphoids the patient in many cases does not refer to that region.

ENTERIC FEVERS

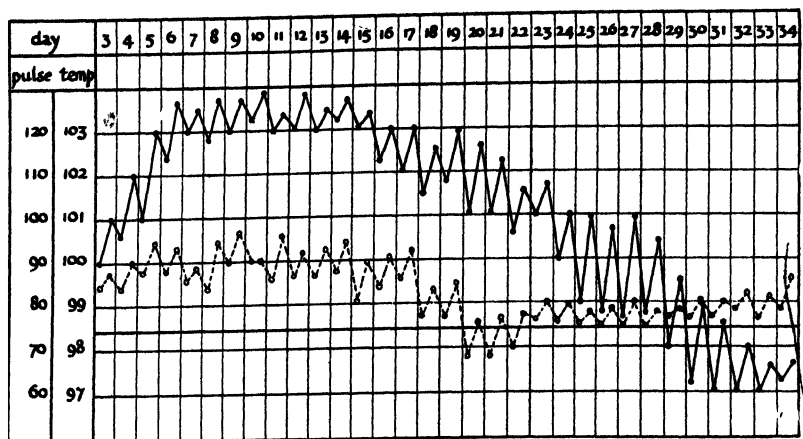


Chart 16.—Typhoid fever, with graph of pulse-rate. *S. Typhi* isolated from blood 6th day; rose spots present and spleen palpable 9th day. (Garrow.)

There may be diarrhoea from the commencement, or diarrhoea followed in a few days by constipation, or the patient may have obstinate constipation from the beginning. The temperature is invariably raised. It may mount step-ladder-like during the first week, or it may rise suddenly, to reach its highest point in the first 24–28 hours, and, after a period of continued fever, begin to remit in the morning and terminate by lysis. A highly characteristic feature of all the enteric infections is the pulse, which is usually soft, often dicrotic, and relatively low (Charts 16–18).

On physical examination, the abdomen may be found more or less distended, as in severe typhoid, or there may be little or no distension, as in the majority of paratyphoids. Splenic enlargement is practically constant, the organ usually

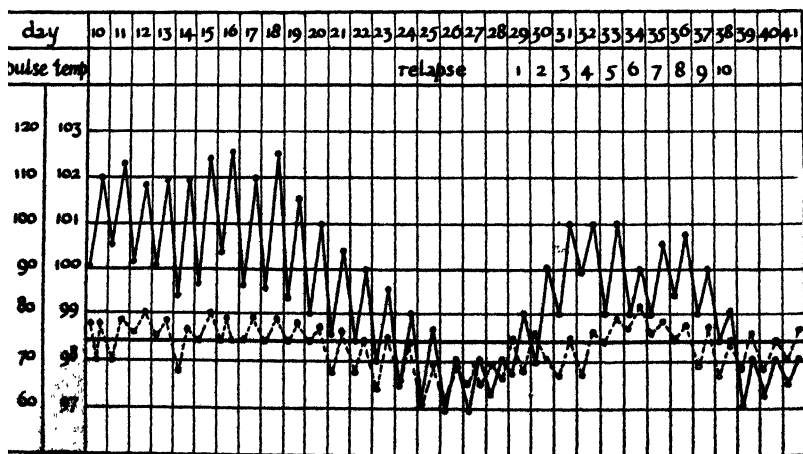


Chart 17.—Paratyphoid-A fever, with graph of pulse-rate. *S. paratyphi B* isolated from blood 16th day, and *S. paratyphi A* on 31st day. (Garrow.)

being large enough, at some stages of the illness, for its lower pole to be palpable below the left costal margin. It may be felt in some cases on the second or third day, if the patient comes under observation so early, or not until the second or third week, or even later. In some cases it becomes palpable for the first time only after the temperature has become normal. Usually about the seventh to the tenth day, but it may be earlier or much later, "rose spots" appear. These vary considerably in number, size, shape, general characters and distribution. There may be only two or three on the abdomen, or the body and limbs may be covered, from the soles of the feet to the scalp. They are of a pale-rose colour, slightly-raised, round or lenticular, and fade on pressure. The more profuse eruptions occur in paratyphoid fever, especially paratyphoid-A. When the eruption is not of this profuse type its distribution is characteristic: 90 per cent. or more of it is on the trunk, between the levels of the iliac crests and the nipples. The patient usually coughs and has a certain degree of bronchitis. Certain features of *S. typhi* infections, as they occur in Chinese, have been remarked upon by Wilkinson, Snapper and others. Multiple rigors are by no means uncommon. Hepatitis typhosa and jaundice, due to empyema of the gall-bladder, are frequent,

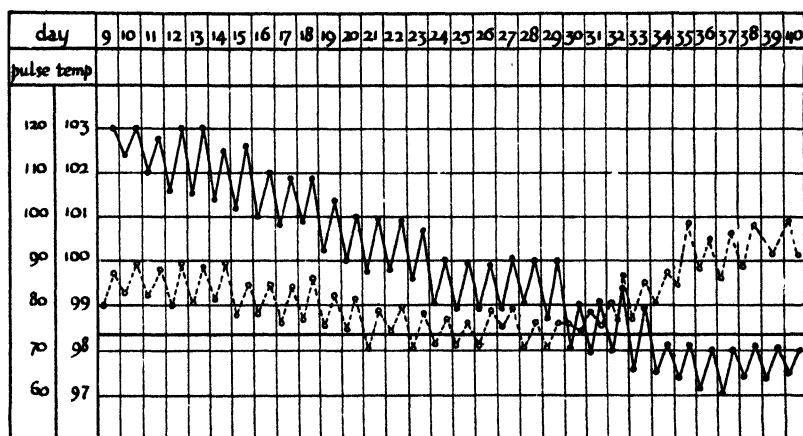


Chart 18.—Paratyphoid-B fever, with graph of pulse-rate. *S. paratyphi B* isolated from blood 9th day. (Garrow.)

whilst hæmorrhage, perforation and phlebitis are rare. The organism has been recovered from the cerebro-spinal fluid in patients with meningeal symptoms. Atrophy of the skin and alopecia are common sequelæ, but a most dangerous complication is the lighting-up of long-standing pulmonary tuberculosis.

Typhoid osteomyelitis of the long bones, especially the tibia, or of the spine is perhaps a more common sequel in the tropics than elsewhere.

DIAGNOSIS

Clinical diagnosis.—(1) *Pyrexia.*—Continued pyrexia of remittent type, ending by lysis, may be regarded as a feature of every case of acute enteric fever (typhoid or paratyphoid). The pyrexia may be high or low, long or short, with remissions great or small. The onset of pyrexia may be gradual or sudden, and lysis may be slow or rapid, thus giving a great variety of temperature charts within the type; but there is no good evidence to show that the fever ever departs from this type. Cases presenting the following features certainly should not be regarded as enteric:

ENTERIC FEVERS

- (a) Temperature is normal or subnormal throughout the entire illness ("apyrexic type of enteric").
- (b) Temperature reaches normal or subnormal at some period of the twenty-four hours on every day of the illness ("intermittent type of enteric").
- (c) Temperature shows perfect tertian or quartan periodicity throughout ("malarial type of enteric").
- (d) Temperature shows a series of short relapses of one to three days' duration, occurring at intervals of a few days ("trench-fever type of enteric").
- (e) The temperature ends by a genuine crisis.

Examples of all these so-called "types of enteric fever" will be found in the literature, the erroneous diagnosis having been based upon the unwarrantable bacteriological or serological finding.

(2) *Low pulse-temperature ratio*.—One of the most valuable diagnostic points is the slowness of the pulse in relation to the pyrexia. The normal pulse-temperature ratio may be tabulated as follows:

Pulse . . .	50	60	70	80	90	100	110	120	130	140
Temperature .	96°	97°	98°	99°	100°	101°	102°	103°	104°	105°

In enteric fever the pulse is, as a rule, 20, 30 or 40 beats per minute slower than thus indicated. For example, it is common to find an enteric patient with a temperature ranging about 103° to 104° F. and a pulse of 90 beats per minute, or it may be even slower. If the pulse is recorded graphically in red ink alongside the temperature curve in black, a very striking clinical feature of great diagnostic significance is clearly brought out.

(3) *Characteristic toxæmia*.—There is something very characteristic in the general appearance, facies, and decubitus of the enteric-fever patient. His disease may in many cases be confidently diagnosed by a glance. He has a dull, heavy, toxin-laden appearance in the early acute stage, with a moist face and flushed cheeks. The experienced clinician at once recognizes the difference between this and the toxæmia of, say, malaria or relapsing fever. In the mildest paratyphoid infections there is little or nothing of this toxic appearance, whilst some infections other than enteric are accompanied by a general toxæmia closely resembling it. Nevertheless, this sign, to the experienced physician, when taken in conjunction with the others, is of diagnostic significance.

(4) *Splenic enlargement*.—As some degree of splenomegaly is practically invariable, this sign is of considerable value in making a diagnosis. Unlike the majority of tropical splenomegalies from other causes (malaria, kala-azar, etc.), the enlargement is acute, so that, even when superadded to a spleen already enlarged from malaria, it has certain exceptional features of diagnostic significance. For example, the acutely enlarged spleen of enteric is tender.

(5) *Rose spots* may appear in the first week, but more often in the second, and tend to come in crops. They may not appear until the temperature is normal. In warm climates, many European skins are apt to show spots more or less like those of enteric fever, as the result of mosquito-bites and of inflammation of hair follicles or sweat-glands. Great care must be taken in discriminating between the true spot and these "pseudo-rose spots."

Summary of clinical diagnosis.—Every undiagnosed fever in the tropics should be regarded as a possible case of enteric fever and closely observed clinically, at the same time that bacteriological and serological investigations are being carried out and Marris's atropine test is applied. While valuable clinical evidence may be obtained from occasional signs, such as epistaxis, pea-soup stools, abdominal distension, and hemorrhage from the bowel, the diagnosis should rest in the great majority of cases upon the presence or absence of the five cardinal signs. Any case presenting the first, second, and third signs should be treated as enteric

(whether the diagnosis is supported by laboratory findings or not) until some other definite diagnosis is made. No case which does not show the first, together with at least two of the remaining four cardinal signs, should be definitely regarded as enteric. Five types of temperature chart have been described, any of which excludes enteric. These, however, imply that the case has had its temperature recorded from the outset, which is not often possible. In the majority of cases of active enteric fever, all five signs are present at one or other stage of the illness.

Finally, it should be remembered that, for every case of enteric fever which imitates some other disease, there are at least a score of cases of other diseases imitating enteric (malaria, phthisis, liver abscess, syphilis, etc.).

Paratyphoid-C.—This, as observed by Giglioli in British Guiana, although essentially a "fever" producing a temperature chart not unlike those of other paratyphoid fevers, is a septicæmia, and the intestinal tract may not be specially involved. Complications such as arthritis, abscess formation and cholecystitis are common, whilst fixation abscesses from intramuscular injections may occasionally contain a pure culture of the bacillus. There appears to be a special connection between paratyphoid-C infection and malaria. The mortality of Giglioli's series of 92 cases of definitely diagnosed paratyphoid-C infections was 38 per cent. Probably a great number of abortive and mild cases passed unobserved. A few cases were reported in the Army in India.

Bacteriological diagnosis of "enteric".—(a) *Hæmoculture* is unquestionably the most satisfactory method of diagnosis; it should be employed, wherever the necessary facilities are available, in every case of undiagnosed pyrexia in the tropics as soon as a blood-film is found to be free from malaria parasites. A successful hæmoculture furnishes the only conclusive evidence that the patient is suffering from active enteric fever, and can hardly be said to be open to fallacy. Unfortunately, however, the usefulness of the method is limited by the short duration of bacillæmia. In many cases which are undoubtedly enteric, negative results are obtained because hæmoculture has been attempted too late. Recent experience has shown that culture from the *blood-clot* gives the highest percentage of positive results. Culture of material obtained by sternal puncture (medulloculture) has been shown to be useful in paratyphoid-B infections, and in China it has proved to be more practical and reliable than blood culture.

Clot-culture.—This method, in combination with streptokinase broth, has been recommended for the isolation of *S. typhi* of suspected early cases. Normal serum in this medium lessens the chances of isolating the organism from clots infected either naturally or artificially. Positive cultures can now be obtained in less than twenty-four hours by culturing clots free from the patient's serum in streptokinase broth put up in 4 oz. bottles containing slopes of Wilson's and Blair's medium.

(b) *Culture of excreta.*—Urine and stools should be plated when blood-culture has failed, and this should be repeated during convalescence to determine whether the patient is free from infection. Bacilluria occurs after the fourteenth day in about 25 per cent. In about 75 per cent. of cases, and, under modern conditions, by employing the brilliant green enrichment method, tetrathionate broth or Wilson and Blair's agar medium for concentrating the typhoid and paratyphoid bacilli, cultivation of the organisms from the faeces in all stages is now successful. Glass and Wright (1937) showed that this method gave a high percentage of results, especially in the early stages; so that during the first two weeks it is more likely to be successful in diagnosis than the Widal reaction. Some positive findings from culture of excreta are open to fallacy. The case may be one of an enteric carrier suffering from some illness other than enteric—e.g., malaria or

trench fever. The detection of carriers can only be effectually carried out in a fully-equipped laboratory; at least seven separate and consecutive bacteriological faecal tests are necessary.

Serological diagnosis.—The *Widal reaction*, or the agglutination of the enteric bacilli by the serum of infected patients, is the most reliable test for diagnosis. The term *antigen* denotes any substance which, when introduced parenterally into animal tissues, stimulates the production of an antibody and reacts with it in some observable way. An *antibody* is a globulin present in the blood serum or body fluids of an animal, usually as the result of the stimulus provided by the introduction of an antigen into the animal, which reacts specifically with an antigen in some observable way.

When used for *uninoculated* subjects it gives a reliable diagnosis in the great majority of cases. However, possible fallacies are that a positive test may result from a previous attack of enteric and a negative result may be obtained in the early stages of the fever; should, however, the clinical manifestations be suggestive, the test must be repeated on several occasions. There are, it is true, exceptional cases of enteric, especially paratyphoid A, which may fail to develop agglutinins in the serum. The modern view about this test is that it must be both qualitative as well as quantitative. In inoculated persons specific agglutinins are produced which are difficult to distinguish from those caused by infection. Thus their recognition has not any diagnostic significance. In recent time differences in the agglutinins have been established. These are known as H and O. Their significance varies and they also differ in their titres, which fluctuates in relation to the progress of the disease.

The enteric bacilli—*S. typhi*, *S. paratyphi* A, B and C—are usually motile and so have flagellar (H) and somatic (O) antigens. The H antigens of these organisms differ from one another, but B and C possess a common "group" phase antigen which is also found in many other organisms of this group (*Salmonella*). The O antigens are also different, but there exists a considerable degree of relation between these, e.g., *S. typhi* and *S. para B*. In order to test for H agglutinins formalized suspensions of the organisms are used, whilst for O agglutinins an alcoholized suspension is substituted. In Europe suspension of *S. typhi* H and *S. para B* H (specific phase) and *Salmonella* H (group phase), *S. typhi* O and *para B* O are used, but in the tropics *S. para A* or C, H and O are included.

Inoculation of normal persons with T.A.B. vaccine produces both H and O agglutinins, the O usually falls to a low level after the lapse of a year or so, but the H agglutinins persist for many years and are liable to be restimulated by various febrile illnesses such as influenza and malaria. This is a most important fact which is often overlooked. It therefore follows that, in inoculated subjects, the H agglutination is of little value in diagnosis, whilst in those who have been repeatedly inoculated the appearance of O agglutinins is also of doubtful value. Significant titres of agglutinins can only be assessed when the local "normal" frequency is known. Generally speaking an H titre of 1 : 50 or over in a patient with fever, and about the 7th–10th day of illness would certainly be diagnostic. An O titre of 1 : 100 or over, whether the patient has been inoculated or not, would also be significant.

In doubtful cases it is necessary to repeat the test in a few days in order to observe whether the titre of agglutinins is rising or not. It was demonstrated by Dreyer and colleagues that, if an estimate is made of the agglutinin content of the serum early in enteric fevers and repeated at intervals of a few days, a steady rise to a maximum, followed by a slower fall, ensues. The maximum titre usually occurs between the eighteenth and twenty-first days of the illness. From recently isolated virulent strains an additional labile body antigen can

be recognized. This is known as Vi antigen which may render the organism insensitive to O agglutinins. In acute clinical infections Vi antigens usually appear early and are extremely transient. The chief importance of this antigen is that it is found in the serum of chronic carriers of true typhoid as well as paratyphoid bacilli. They thus constitute a useful pointer to a possible carrier state, indicating that intensive bacteriological examination of faeces, urine and duodenal juice must be undertaken; they can also be used as an additional test in proving that a person is free from infection before discharge from hospital. Vi agglutinins differ from the others in that they are not stimulated by the vaccines of T.A.B. which are commonly employed and which are killed by heat and preserved with phenol. They may, however, be produced by the newer alcoholized vaccines. It has therefore become apparent that the original claims made by Felix that H, but not O agglutinins are produced as the result of passive inoculation, and not as the result of infection by living organisms, now requires further confirmation.

Auxiliary method of diagnosis.—The diazo-reaction in the urine is useful, but may be present in malaria. Russo's methylene-blue test is said to be more conclusive, as it is absent in malaria.

Differential diagnosis.—The abdominal pain of enteric may be mistaken for *appendicitis*, but the matter may easily be settled by a leucocyte count, which in the former shows a leucopenia with a relative lymphocytosis, and in the latter an active leucocytosis. *Bacterium coli infections* may resemble enteric. *Typhus* is notably difficult to distinguish in its earlier phases, though the leucocytosis in that disease may be of considerable assistance.

It must not be forgotten that enteric fever may co-exist with some other acute infection such as malaria.

Treatment.—All that the great majority of mild paratyphoid cases require is a soap-and-water enema every other day to relieve the constipation. Milk should be the diet while the patient is febrile; thereafter custard, milk pudding, soup, fish, and meat diet. The diet should contain about 70 gm. of protein a day, with a caloric value of 2,500–3,000. Water should be given freely. Purgative medicines should be avoided. The care and cleanliness of the mouth and teeth are important.

In cases marked by great toxicity with high temperature (over 102.5° F.) and no morning remissions, tepid sponging is beneficial; in the worst cases the cold bath or ice pack may be used. The temperature of the water should be between 70° and 85° F.; a tub of canvas and mackintosh sheeting may be improvised. Food may be given as a stimulant after the bath. The rectal temperature should be taken immediately on removal from the water, and again three-quarters of an hour later.

Felix's antiserum treatment.—Working on his observations on the virulence of smooth strains of *S. typhi* towards the "O" antibody and the Vi antigen which is definitely associated with virulence, Felix (1935) produced an efficient antiserum from horses by injecting the Vi antibody. The therapeutic effects of this serum have been tested in a number of cases in Palestine and in Dublin.

Chloromycetin (chloramphenicol).—*In vitro* this antibiotic inactivates *S. typhi* in 0.25 mgm. per ml. Those treated by Woodward and colleagues in Malaya (1948) with initial oral dosage of 50 mgm. per kg. body weight, thereafter 0.25 mgm. every two hours till the temperature was normal, did well and the mean duration of fever was 3.5 days after treatment. It is agreed that the treatment should extend over 14 days at 50–100 mgm. per kg. daily.

Smadel (1954) asserts that, before the introduction of chloramphenicol, the mortality from typhoid was about 10 per cent. and about a quarter of deaths

were due to toxæmia. With chloramphenicol alone there is a danger that this toxæmia may be temporarily increased so a series of 18 cases in Malaya were treated with chloramphenicol concurrently with cortisone from the 9th–16th days of the disease. The dose was 3 grm. given initially, followed by 1.5 grm. every twelve hours till forty-eight hours after defervescence. The cortisone was given in 10.7 mgm./per kgm. for one day. Whereas normally it took four days before defervescence under the antibiotic alone, combined chloramphenicol and cortisone produced dramatic and rapid effects. The average time was six hours and signs of toxæmia diminished. In a small proportion of cases there was an ensuing hypothermia. The sulphonamides—sulphadiazine especially—have proved efficacious.

In hæmorrhage, all fluids should be stopped for at least 48 hours, and sufficient morphia injected to keep the patient at rest. Though a very large amount of blood may be lost without causing a fatal result, yet, when feeding is recommenced, it should be proceeded with very carefully. As a general rule, one large hæmorrhage is less serious than a number of smaller ones. When bleeding has ceased, a subcutaneous infusion with saline up to 1½ pints may be permitted, and this may be repeated later should no further hæmorrhage occur. Blood transfusion has been employed with advantage and appears to arrest the hæmorrhage. It is advisable, should hæmorrhage be suspected, to give 30 gr. of calcium lactate three times daily; some make a practice of doing so from the sixteenth to the twentieth day of a typhoid fever, and from the fourteenth to the eighteenth day of a paratyphoid. In thrombosis, sodium citrate is indicated.

Prophylaxis.—*Anti-enteric inoculation* has been conspicuously successful, as shown by the statistics of the American Army, and of the British Army in India. During the 1914–18 war the vaccine was modified by the introduction of *S. paratyphi-A* and *-B*, and the statistics furnish conclusive evidence of the efficacy of this measure of prevention, not only in lessening the incidence, but also in modifying the disease or diseases. Therefore, everybody proceeding from a country such as England to the tropics or subtropics should be inoculated with two doses of triple vaccine (T.A.B.), and should be re-inoculated every year subsequently with one “booster” dose, 1 ml., so long as he remains in a country where enteric is prevalent.

The official vaccine contains 1,000 millions of typhoid bacilli, 750 millions of paratyphoid-A, and an equal number of paratyphoid-B, to each c.c. Two doses of 0.5 ml. and 1 ml. are given at an interval of ten days. The reaction in the majority of instances is slight. Occasionally, however, cases of persistent pyrexia with severe local symptoms, malaise, and headache are met. In countries where paratyphoid-C is prevalent a tetravalent vaccine should be employed.

Vi antigen.—Felix has shown that in typhoid and paratyphoid formalin (commonly used for killing cultures) has a definite deleterious action on “O” antigen which is concerned with typhoid immunity, whereas heating to 60° C, or higher, leaves this antigen intact. Another antigen of typhoid—the Vi antigen—which Felix maintains is connected with typhoid immunity, is destroyed by heating to 60° C, or by formalin, but can be preserved by killing the bacteria with 75 per cent. alcohol.

Vi alcohol-killed vaccine is under trial. The vaccine retains its power after storage in the cold for at least nine months. Felix, Rainsford and Stokes compared this Vi vaccine (T.A.B.) with ordinary heat-killed T.A.B. and T.A.B.C. vaccine from various sources. Two marked differences were found between groups of subjects inoculated with the two types: alcohol-killed and preserved vaccines stimulated demonstrable Vi antibodies in a relatively high proportion, whereas the Vi antibody response to ordinary vaccines is negligible. No signi-

ficant difference in O antibody response was observed. Reactions produced by alcoholized vaccines were milder than by the ordinary method.

Felix's Vi Vaccine contains :

1,000 million *Sal. typhi*.

500 million *Sal. A, B, C.* per ml.

<i>Dosage.</i>	<i>1st dose.</i>	<i>2nd dose</i>
Adult males	0.25 ml.	0.5 ml.
„ females	0.2 „	0.4 „
Children		
16-18	0.2 „	0.4 „
13-15	0.1 „	0.2 „
9-12	0.05 „	0.1 „
under 8	0.05 „	0.05 „

Interval between injections: three weeks; revaccination advisable one year after primary immunization. The injections should be made as late as possible in the day.

ENTERIC-LIKE FEVERS

Septicæmia due to *Bacterium alkaligenes* and other organisms.—A series of mild pyrexias, of either remittent or intermittent type, has been proved by Hirst and others to be due to infection with *Bact. alkaligenes* (Table VII, p. 477). It is a common inhabitant of the intestinal canal, where it is not definitely known to exert any pathogenic action. The fever it gives rise to in the blood-stream may last from two to fifteen days. There is an evening rise with marked morning remission. The symptoms resemble those of a mild enteric, the pulse is slow in relation to the temperature, and the tongue is slightly furred. In some cases the patient's serum agglutinates the homologous organism in a dilution of 1 in 50.

In outbreaks of food-poisoning or "ptomaine poisoning," which occur from time to time, bacilli of the *Salmonella* group, *Sal. enteritidis*, *S. suispestifer*, have been isolated from the bloodstream. The fevers they produce have many features in common with enteric. They differ in the suddenness of the onset, with rigors, the accentuation of the gastro-intestinal symptoms, the short duration and rapid termination of the fever. *S. suispestifer* resembles *S. paratyphi-B* in its biochemical, but may be differentiated by its serological reactions.

Bacterium (Escherichia) coli infections.—Infection of the bladder and urinary tract with *Bact. coli* is frequently met in both sexes in the tropics. Should the organism enter the bloodstream it may give rise to a prolonged intermittent pyrexia resembling enteric. *Bact. coli* septicæmia and pyæmia may be a terminal infection in debilitated persons, especially as a sequel of bacillary dysentery; in these cases the organisms gain entrance to the bloodstream through the intestinal lesions, and, becoming arrested in the glomeruli, give rise to multiple and minute abscesses in the cortex of the kidneys, from which they escape intermittently and appear in the urine (Fig. 60). The condition, which was first described in Egypt by Enright and the Editor, has now been found fairly commonly as a sequel of bacillary dysentery in the Middle East. The general condition of the patient, the stupor and the intoxication, may resemble those of enteric, but the onset is generally sudden, with headache, and acute pain referred to both kidney regions. Usually vesical irritation is absent. The tongue is thickly furred; rigors are numerous and accompanied by profuse sweats. The organism may be recovered in pure culture from the bloodstream during the rigors, as well as from the urine by ureteric catheterization. The acute attacks are apt to be confused with those of malaria. This form of *Bact. coli* infection is amenable to sulphonamide (sulphapyridine and sulphadiazine) treatment and streptomycin.

Pyelitis.—It was formerly considered that the anatomical relationship of the renal pelvis to the colon determined the frequency of infection, especially in women, but Leishman (1939) found that looseness of the bowels was the most frequent determining factor, suggesting an ascending infection. The symptoms may commence with a rigor and a dull aching pain in the loins which is increased

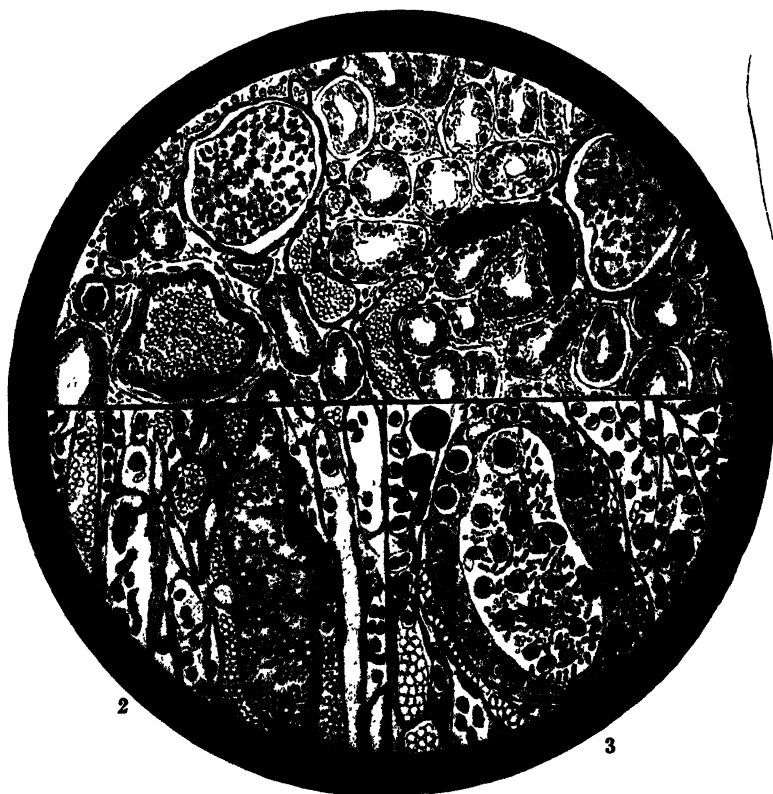


Fig. 60.—Sections of kidney in *Bact. coli* septicæmia.

1, Aggregation of organisms in intertubular capillaries; 2, large collection of organisms in a medullary vein; 3, passage of bacilli through tubular epithelium of duct of Bellini into lumen.

on pressure. Micturition may be frequent, and sometimes a large and tender kidney may be palpated. The results of the inflammation are soon seen in the urine, which contains albumin, pus cells, and sometimes even blood. *Bact. coli* is present in large numbers, especially in the first specimen of urine passed during the day. Differentiation from malaria, which it may closely resemble, may be necessary. *Cystitis*, with pyrexia and acid urine, may also be due to *Bact. coli* and is very apt to occur as a sequel to any debilitating tropical fever, especially enteric infections. It is always necessary to consider this possibility. *Bact. coli* infections of the urinary tract are quite commonly engrafted upon some other more serious infection, such as tuberculosis, and may mask the

original picture of this disease. The possibility of ascending infection of the ureters from a long-standing prostatitis or urethritis in the male must not be ignored. In women this may be a sequel of miscarriage or parturition.

Treatment.—Sulphonamides are especially useful in *Bact. coli* cystitis, pyelitis and trigonitis. Sulphapyridine and sulphadiazine in doses up to 3 grm. daily for 10–14 days may be reinforced, if necessary, by after-treatment with mandelic acid preparations. A better preparation is “Steramine,” which is sulphacetamide¹ (N₁ acetyl derivative of sulphanilamide). It possesses a low toxicity with high antibacterial activity. In most acute cases the dose is 2 grm. initially, followed by 1 grm. four-hourly for two days, then 1 grm. six-hourly for two days and finally 1 grm. eight-hourly for a further two days. In obstinate cases treatment lasting 10–14 days may be necessary. Intravenous injections of 5 ml. of a 30 per cent. solution may be given at the commencement of the course. Streptomycin when injected in full doses gives good results in sterilizing the urine and aureomycin has much the same action.

It must be emphasized that, in employing these therapeutic measures, the condition of the kidneys and ureters should first be ascertained by means of excretion urography (uroselectan). Sometimes a calculus may be discovered in the renal pelvis or in the ureters, which may be the seat of the *Bact. coli* infection, necessitating surgical intervention.

¹ Albucid is the alternative trade name

Subsection E.—DISEASES CAUSED BY VIRUSES

CHAPTER XVII

YELLOW FEVER

Synonyms.—Typhus icteroides ; Fièvre jaune ; Fiebre amarilla (Spanish) ; Gelbfieber. “Amaryl”—International nomenclature.

Definition.—An acute, specific febrile infection, due to a filterable virus, occurring epidemically, or endemically within a limited geographical area. It is primarily an infection of monkeys in which it is largely asymptomatic. Though subject to great variation and occurring sometimes in a mild form, both in Africans and in Europeans, its typical clinical manifestations may be said to be a sthenic initial stage, rapidly followed by an adynamic condition. Jaundice and albuminuria commonly occur. One attack confers immunity for life. The virus is transmitted principally by female aëdine mosquitoes, which remain infective during their lifetime.

Geographical distribution.—At present yellow fever is mainly confined to South and Central America, and in Africa south of the Sahara from the Atlantic Coast to the Red Sea and Indian Ocean (Map VII). In comparatively recent times it is known to have been widespread in the West Indies, Mexico and in the United States, as far north as Philadelphia (1793) and Memphis (Mich.) (1878), and as far south as New Orleans and Galveston (1905). During the last century it was imported from time to time by ships to the Canary Isles, Spain, Portugal and to the small islands of Ascension and St. Helena in the South Atlantic, in all of which limited outbreaks took place. In 1865 a few cases occurred in Swansea, South Wales. The disease has never invaded Asia or Australia. It is still by no means certain whether yellow fever originated in West Africa and was conveyed by ships to the West Indies and South America, or whether the disease was enzootic in America before the coming of man.

In South America yellow fever was endemic in Brazil, Bolivia, Colombia, Peru, Venezuela and Guatemala, and there is some evidence that it still exists in British and Dutch Guiana. In their campaign against yellow fever the Rockefeller Foundation concentrated on eradicating the “seed-beds of infection” on the South American continent in the belief that they were few. The clearing of Rio, Santos and Nitheroy was followed by apparent disappearance of yellow fever from the whole of Southern Brazil. After a campaign in Guayaquil and another in Peru in 1920, no further cases were recorded on the Pacific Coast. Similar results were obtained in Colombia, Mexico and Central America. Yellow fever reappeared in Panama in 1948–1949 after an absence of forty years when cases of the jungle variety were diagnosed (Herrera).

In 1928–1929 yellow fever reappeared in Rio de Janeiro. Soon locally infected cases occurred in the Brazilian States of São Paulo, Minas Geraes, Rio, Bahia, Sergipe, Pernambuco and Para. In 1932, by the introduction of the *viscerotome*, an instrument for obtaining liver tissue for examination,



MAP VI
Distribution of Yellow Fever in Africa

it was possible to prove the existence of "jungle yellow fever" (in the absence of *Aedes aegypti*) in Espirito Santo. This is now regarded as the original and more permanent form of yellow fever. In West Africa yellow fever has long been known from Senegal to the Congo, while the long story of British endeavour in the development of this country, especially Sierra Leone and the Gold Coast, is one of struggle against yellow fever. (In 1826, out of the garrison of 535 soldiers, 115 were dead within two months, while of the first detachment of troops which occupied Cape Coast Castle in 1823 only one man was alive a year later. In 1878 an epidemic involved the whole of Senegal, affecting 1,474 Europeans.)

In the epidemic in Accra in 1937 the native population and Syrians were alone affected. Small outbreaks took place on the Congo at Matadi and Boma in 1927 and 1928, at Bathurst on the Gambia in 1935, and there were numerous other cases in Ghana and in Nigeria in 1937 and 1938. The most extensive epidemic of yellow fever recorded in Africa

broke out in the Nuba Mountains, Southern Sudan, in May, 1940, and there were 17,000 cases with a mortality-rate of 10 per cent. Previous to this, one single case of yellow fever had been recognized at Malakal in 1934. The epidemic subsided in November and was followed by a rise in the proportion of immunes in the population.

An epidemic confined to non-Europeans occurred in Nigeria in 1946 and in 1951 in the northern Province.

Recent Information.—The fact that severe and fatal cases have not been seen, or recognized, does not warrant the assumption that an area is free from this infection.

In *Ghana* in 1955 there were three deaths within 8 days and four others were confirmed in laboratory at Kitampo. The hæmagglutination inhibition test (HAI) of Porterfield was employed.

In *Central Africa* in 1940 yellow fever was reported at Yatolema near Stanleyville, in Northern Rhodesia in 1943 at Balovale, in Southern Rhodesia on the Zambesi River and in North West corner near the Angola border.

Anglo-Egyptian Sudan.—Additional evidence from the Fung area has shown that yellow fever has recently occurred as far East as the Abyssinian border. In the equatorial province, East of the White Nile, yellow fever is widely distributed. A fatal case in a European was reported in Torit in 1942 and also one in Kapoeta. Immune sera have been found in the Imatong tribe in the Imatong Mountains.

In Southern Abyssinia one protective serum has been obtained.

Eritrea.—The evidence is that yellow fever has recently occurred in coastal areas and in the western plains, near the Red Sea coast, and also in Somalia.

Kenya.—A fatal case occurred in Kitale in 1942 and a second in 1948. Immune sera have been found in the adjoining Langata forest.

A fatal case, the fourth in E. Africa, was reported in *Uganda* in 1953.

In 1957 there were three cases in the Belgian Congo and two suspected ones in Nigeria.

It has now been shown, as the result of immunity surveys, that yellow fever extends in a region from St. Louis on the coast of Senegal, just north of Cape Verde, eastward at latitude 15° N. along the southern borders of the Sahara through El Fasher to Dilling in the Southern Sudan. Thence the line bends southwards at Rashad in the Nuba Mountains, crossing the White Nile south of Jelebein, passes through Dar Fung, the area between the White and Blue Niles, up to and possibly beyond the Sudan-Abyssinian border. An extension eastward has been established to the N.W. boundary of Eritrea and the Red Sea coast, thence S. to the border of Somalia, at 36° meridian of longitude, south of Lake Rudolf. The eastern border runs through Western Uganda to the west of Lakes Victoria and Tanganyika, and thence diagonally at 10° S. parallel, across the Belgian Congo to the mouth of that river. In the west the line follows the Atlantic coast from Senegal to Santo Antonio in the extreme north of Angola: a total area comprising approximately four million square miles. The islands in the Gulf of Guinea are included as well as the Balovale district of Northern Rhodesia and part of Bechuanaland. (Map VII.)

In the Western hemisphere the endemic area is bounded by a line running from Turbo in North Colombia directly south to the northern boundary of Ecuador and thence along the eastern slopes of the Andes, below an elevation of 6,000 feet, to the northern boundary of Argentina; thence east along the twenty-second parallel of latitude to the west border of Brazil, thence in a north-east direction to the junction of the states of Maranhão and Pará on the Atlantic Coast of Brazil, and thence along the Atlantic and Caribbean coasts of South America to Turbo. In addition the Isthmus of Panama, from the canal zone to the border of Panama and Colombia, and the Ilheus and Itabuna districts in the state of Bahia in Brazil are regarded as endemic areas. (Map VIII.) Seventy-four cases of jungle yellow fever were notified in America in 1957, the majority in Colombia, Bolivia and Brazil.

Jungle yellow fever in Central America.—At the end of 1948 yellow fever appeared in Panama to the east of the Canal. It then spread to Costa Rica, where the virus was isolated, and subsequently in San José, the capital, there were at least 40 autopsies. This was the starting point from which it spread to Nicaragua. From July, 1952, whilst the fever simmered amongst the rural population, there was an outbreak amongst the howler monkeys (*Alouatta stenor*) and large numbers died. The spread of yellow fever in man and monkeys travelled at the average speed of 13 miles per month and the wave took two months to pass any particular spot. Certain species of *Hæmagogus* and *Aedes leucocelænus* were present. In this case the epidemiology followed the pattern already worked out in the basin of the Amazon and was confined to lowland forest so that it failed to establish itself in cities, presumably because of the elimination of *Aedes ægypti*. This epidemic came to an end in 1954.

In Trinidad there was a sharp outbreak between April and October, 1954. There were 15 human cases and four deaths. The virus was isolated from all but one. In January, 1955, it was obtained from the livers of seven red howler monkeys (*Alouatta seniculus insulanus*) while in the blood of others, as well as in *Cebus apella*, antibodies were found and the virus was obtained from pools of *Hæmagogus spegazzinii* (Downs, Aitken and Anderson).

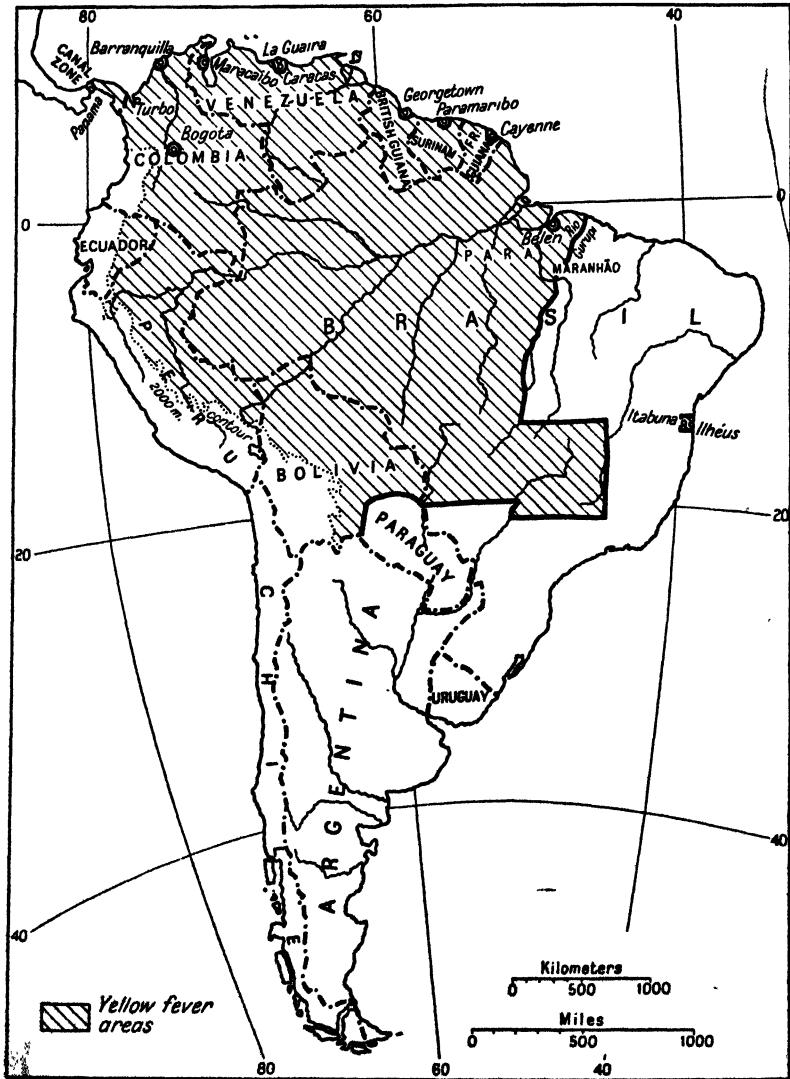
Finally, it is obvious that the geographical distribution of yellow fever does not correspond with that of *A. ægypti*, as the Orient, with its susceptible population and abundance of suitable mosquitoes, has so far remained free.

Epidemiology.—In former times it was generally considered that yellow fever was mainly confined to seaports and that it seldom spread far inland, but this is now known not to be the case. A study of epidemics shows that the virus of yellow fever can be readily transported from one place to another and that for its development in the mosquito it requires, usually, a mean atmospheric temperature of 75° F. (24–25° C.), and that endemic centres have never extended beyond 40° N. Lat. and 35° S. where the isotherm is not below 68° F. (20° C.). A high wet-bulb temperature favours yellow fever, so that it is most likely to arise and spread during the rainy season. It may, however, be found in mountainous regions up to 4,000 ft. In spreading inland it appears to follow lines of communication.

Conceptions on the epidemiology of yellow fever have had to be con-

siderably revised since the discovery of the jungle form. Some authorities recognize three divisions—urban, rural and jungle—the last of which is thought to be the most primitive. Soper, on the other hand, favours the following classification:

(1) The urban and rural types are a domestic and purely human disease with a simple cycle of infection depending upon man and the insect vector,



MAP VII
Distribution of Yellow Fever in South America

Aedes aegypti, but these forms cannot spread in the absence of *A. aegypti* mosquitoes in sufficient numbers.

(2) Jungle yellow fever, involving man and animals, in the absence of *Aedes aegypti*, indicates that neither this insect nor man himself is an essential element in the insect-vertebrate cycle of infection which maintains the reservoir of the virus in the jungle.

Junglé, or Sylvan, Yellow Fever.—It is now known that this form of yellow fever is conveyed by the bites of certain jungle mosquitoes (in Bolivia, Colombia and Brazil by *Aedes leucocelænus*, *Hæmagogus spegazzinii falco* and possibly also *Sabethoides* mosquitoes). There is now little doubt that jungle yellow fever exists also in Africa, where isolated cases have been found in the bush. The most important focus about which we have definite information was discovered by Mahaffy and his colleagues in 1941 in North Uganda, on the Semliki, west of Ruwenzori and on the eastern reaches of the Ituri river (Bwamba country). The northern half of this country is heavily forested, uninhabited except for pigmies. There the virus of yellow fever was isolated from humans as well as from a wild-caught mosquito—*Aedes simpsoni*—which appears to be the vector in this area.

Bwamba lies in the extreme west of Uganda bordering on the Belgian Congo and is a lowland forest area bounded by the rivers Semliki and Lamia as well as by the Ruwenzori mountains. The population is sparse on the mountain slopes and grassy plains, but more dense in the cultivated strips in the foothills. The fertile area is crossed by mountain streams. Larvæ of some tree-hole breeding mosquitoes occur in rot holes in soft-wooded figs and in pools enclosed in their buttress roots, but not in water held in fallen leaf tracts of the umbrella tree (*Musanga smilhi*). Outside, the forest fig and *Cassia* plantations are the haunts of tree-hole breeders. The climate is warm and fairly equable. The highest temperature recorded is 98° F., but it rarely falls below 15° C. (59° F.). Humidity is high and approaches saturation during the cooler parts of the day.

The annual rainfall is 50–60 inches, occurring in two rainy seasons, vernal and autumnal equinoxes.

The evolution of epidemics of yellow fever.—In experimental infection of humans the shortest incubation period recorded is about two days, but under natural conditions, it is from one to six and a half days. A period of at least fourteen days may elapse between the arrival of a yellow-fever-stricken patient in a hitherto uninfected district and the first case of the epidemic to which he may give rise. This would indicate that the period between the introduction of the virus into the body and the development of fever is usually some three to five days, yet a period of at least twelve days must elapse before that virus, removed from the human body, can be transmitted by mosquitoes to another man. This is known as the *extrinsic period* and represents the time taken for the virus to multiply inside the mosquito, though experiments with these insects, when fed on monkeys, show that this may be reduced to eight or nine days at high temperatures; at low temperature the mosquitoes *may never become infective*.

Animal reservoirs of the virus.—In 1914 Balfour drew attention to the great mortality amongst red howler monkeys (*Alouatta seniculus*) which preceded outbreaks of yellow fever in Trinidad and Venezuela. Amongst the natives the belief was strongly held that this presaged a human epidemic. In 1935 monkeys

with immune bodies to yellow fever were discovered both in South America and in Africa. Then Soper (1938), in an outbreak in the States of Minas Geraes and Rio de Janeiro, found increased mortality amongst these monkeys and, by protection tests, that they constituted an important factor in the spread of jungle yellow fever in Brazil (Fig. 61). As the result of more recent work in South America it has been shown that inoculation of the virus into certain wild animals produces no appreciable illness, though it is still present in their blood for some days. Such animals are monkeys, marmosets, opossums of all species, especially *Didelphis marsupialis*, ant-eaters, sloths, armadillos, the agouti (*Dasyprocta aguti*), paca (*Cuniculus paca paca*), capybara and some mice. Their movements are not restricted, and so the virus can spread over a wide area; transmission is then probably effected by jungle mosquitoes.

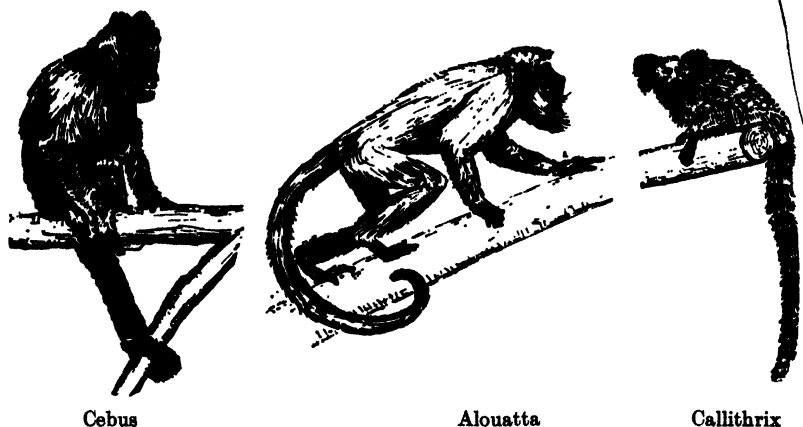


Fig. 61.—S. American monkeys. (Rockefeller Foundation Report.)

Mahaffy regards jungle fever as primarily a disease of primates in the forest and is spread by *Aedes africanus* but, the arboreal monkeys raid the plantations of the neighbouring Africans for food and, in doing so, they come into contact with *Aedes simpsoni* which may become infected from them and in this manner spread the disease to man. This mosquito too may also enter the forest for a blood meal. In this instance *Aedes aegypti*, though present, apparently plays no part in the cycle.

In Central Africa there is some suggestive evidence. Pruner's hedgehog (*Atelerix albiventris*) has been found very susceptible to yellow fever, and the presence of immune bodies in the blood of a monkey, *Colobus badius waldroni*, was verified by Findlay in Ghana in 1935. He, moreover, showed that the sera of about 25 per cent. of the monkeys in Central Africa are protective.

It seems, therefore, that in rural and in jungle areas yellow fever may persist in the absence of susceptible humans. These findings seem to show that there are other methods of spread than by the mosquito-man cycle. Animals which may be concerned with the transmission of yellow fever may be classified as follows:—

- (1) Animals which on inoculation develop symptoms and die with lesions.
- (2) Vertebrates which allow multiplication of the virus in the blood and develop immune bodies.
- (3) Vertebrates which have been shown to harbour virucidal bodies in the blood under natural conditions.

The virus has been isolated from the blood of wild marmosets—*Callithrix penicillata*, *Hapale jacchus* and *Lentocebus chrysomelas* at Ilhéus, Bahia, Brazil; and cyotic passage obtained in *C. aurita* and *Cebus* monkeys—*C. versutus* in combination with *Aedes aegypti* and *Hæmagogus equinus*; a Colombian strain has been maintained with Saimiri monkeys and *H. spegazzinii falco* as vector.

More recently typical yellow fever lesions have been found in the Douroucouli—*Aotus trivirgatus*—and the virus transmitted to Saimiri (squirrel) monkeys (*S. Uta*). This is an important epidemiological fact as the former is the only monkey found in certain areas of Colombia.

In that country too *Oedipomidas œdipus* is the common marmoset, and the virus is transmitted from it to *Aotus* and Saimiri by the bites of *Hæmogogus*.

In Bwamba, Uganda, the general incidence of immunity of monkeys is 61 per cent. The lowland *Colobus* monkey (*Colobus polykomos uellensis*) is the main species involved in monkey to monkey yellow fever cycle, but the red-tail (*Cercopithecus nictitans mpangæ*) plays an important part in bringing the virus into contact with man.

According to the list given by Corson (1945) the following vertebrates are to some degree susceptible to the yellow fever virus:—

Africa and Asia.—*Pan satyrus*—Chimpanzee. *Macaca sylvana*, Barbary ape. *Cercopithecus æthiops centralis*, African grivet monkey. *C. tantalus*, Tantalus monkey. *C. diana diana*, Diana monkey. *C. patas*, Patas monkey. *C. ascarius schmidtii*, Schmidt's white-nosed monkey. *Colobus polykomos*, King *Colobus* monkey. *C. badius*, Bay *Colobus* monkey. *C. b. waldroni*, Waldron's *Colobus*. *Papio cynocephalus*, Yellow baboon. *Macaca mulatta*, Rhesus monkey. *M. irus*, Crab-eating macaque. *Galago senegalensis*, "Bush baby." *G. demidovii*, "Lesser Bush baby." *Erinaceus europæus*, Hedgehog. *Atelerix albiventris*, Pruner's hedgehog.

South America.—*Cebus fatuellus*, Brown capuchin. *C. apella*, Weeper capuchin. *C. xanthosternus*, Small-headed capuchin. *Callicebus ornatus*, "Titi" monkey. *Ateles paniscus*, Red-faced spider monkey. *Alouatta seniculus*, Red howling monkey. *Saimiri sciurea*, Squirrel monkey, *S. orstedii* (Panama). *Aotus trivirgatus*, "Douroucouli." *Lagothrix lagothrica*, Humboldt's woolly monkey (Colombia). *Didelphis marsupialis*, Common opossum. *D. nudicaudatus*, Rat-tailed opossum. *Metachirops columbianus*, Brown-masked opossum. *Caluromys laniger*, Woolly opossum.

Dog, fox, ox, sheep, goat, pig, camel and horse in Africa and South America; also:—

Thryonomys swinderianus, Great cane rat in Africa. The following birds: *Bulbulcus ibis ibis*, African cattle egret. *Tyto alba affinis*, Barn owl. *Halcyon senegalensis*, Senegal kingfisher. *Neopelicanus rufescens*, Pelican. *Anastomus lamelligerus*, African openbill. *Strutho camelus*, Ostrich, and various *Cathartidae*, vultures in South America.

The full significance of virucidal bodies in sheep, cattle and birds requires further study.

All susceptible animals are characterized by a similarity of behaviour following virus inoculation. There is a preliminary clearance of virus from the blood-stream and after a few days it again reappears. Coincident with this later phase antibodies appear and gradually increase to a maximum extending to several months. There appears then to be no virus reservoir amongst non-human vertebrates. The demonstration of the susceptibility of an animal in the laboratory tells little or nothing about its actual part in the natural cycle of the virus. All primates are susceptible to yellow fever, although there is a wide variation in the severity of the yellow fever so produced. Although

certain rodents are susceptible, they play no part in the forest cycle of yellow fever.

Immunity rate.—In areas outside the present known endemic zones of yellow fever, with few exceptions, no immunity against yellow fever exists. Thus, Sawyer and his colleagues showed that, of 876 human sera from Asia and Australia, only 2 gave any protection, whilst amongst 481 sera from Italy, Portugal, Canada and Northern United States of America, even from some of the localities where yellow fever was formerly present, one only was protective. Sera were also tested from the West Indies, Barbados, Jamaica, St. Lucia, Trinidad, Cuba and Porto Rico. The sera of 821 people under twenty years of age were all negative, but above that age 8.42 per cent. gave positive protection tests. These results agree with the fact that yellow fever existed in all these regions until comparatively recent times. In Mexico, however, a higher percentage was obtained. From five to nine years, 0.9 per cent. were positive, from ten to fourteen years, 8.55 per cent., from fifteen to nineteen years, 28.81 per cent., but from twenty years and over, 42.72 per cent.

The results from the Sudan are of special interest as showing that outbreaks of yellow fever can to some extent be predicted. Villages in the Nuba Mountains, which had previously been shown to have a high percentage of immune bodies, were not attacked in the 1940 yellow fever epidemic, and in many 70 to 80 per cent. of positives were obtained, as also in the Fung area to the east of the White Nile.

Investigation of an area, immediately after the subsidence of an epidemic, by means of the mouse protection test, reveals that the number of persons who give positive protection is much greater than the actual number of cases clinically diagnosed as yellow fever.

In Central African forest the general immunity rate amongst the monkeys is very high. Over 40 per cent. are protected. Immune monkeys are found in all parts of Uganda with the exception of Ruwenzori Mountain forest. The highest rate is found in Bwamba county, Toro district and part of Masaka and Mengo districts.

The exclusively arboreal and mainly arboreal species show no significant difference in the incidence of immunity but on the whole terrestrial monkeys show a definitely lower immunity rate.

The high mortality in monkeys is characteristic of the Trinidad and Central American epidemics in contrast to those in South America. The reason lies in the monkey population of these two areas. In the south, especially in central and southern Brazil, the common is *Cebus*, howler and spider monkeys are rare. The former can harbour the virus but does not die of the infection. In Central America *Alouatta* (howler) and *Ateles* (spider monkey) are most abundant, and being susceptible, they die in large numbers. In Nicaragua it seems to have exterminated them, and when they have been thus destroyed, it takes decades to produce a fresh receptive population, but since *Cebus* does not succumb, this monkey in a few years provides a population which is capable of spreading the infection. In Brazil, therefore, these inter-epidemic periods are relatively short. In Central America, when monkeys become scarce, other mammals, such as opossums act as jungle reservoirs.

Vectors.—In Panama, Costa Rica and Nicaragua transmission of yellow fever is related to the presence of *Hæmagogus spegazzinii falco* which inhabits the rain forest. In Honduras the situation is not so clear, because monkeys dead of the fever have been found where this species of mosquito does not exist. A given species may behave quite differently in two different places and even at different times in the same place. The fact is that the results of laboratory experiments are not unreservedly comparable with what takes place under natural surroundings.

On the Atlantic coast, the tropical forests favour the persistence of the insect vectors throughout the year, but on the Pacific side the deciduous tropical forests which result from a long dry season would seem to be unfavourable for the survival of the mosquitoes as well as of the virus, but the virus did survive in the area. At the beginning of the rainy season, 5-6 months later, monkeys began to die precisely where the epizootic had halted. What acts as a reservoir of virus, in the absence of mosquitoes from November to April, has not been ascertained. It remains to be seen whether, with the destruction of some monkeys and immunization of other susceptible species, yellow fever will disappear or whether a permanent reservoir of infection will be formed as already exists in certain parts of Colombia.

In the 1948 outbreak there was a cyclical fluctuation in the density of canopy mosquitoes. The population density of *H. spegazzinii falco* may be much more marked in a particular month of one particular year than in the same month of another.

Ætiology.—The true nature of the virus was adumbrated by Reed, Carroll, and Agramonte who, in 1901, showed that it was filterable and ultramicroscopic. This was the first occasion in which it was proved that a filterable organism might be the cause of human disease. In 1929, Stokes, Bauer and Hudson clearly proved that the agent is ultramicroscopic and passes through Berkefeld filters V. and W. In 1933 Findlay and Broom, by employing Elford's system of ultra-filtration, were able to measure the particles of the virus. Findlay and Broom estimate the size of the particles as 18-27 m μ . Sellards and Hindle showed that the yellow fever virus can maintain its vitality when frozen. When transported from Dakar to London the disease was reproduced in macaque monkeys by subcutaneous and intraperitoneal inoculation. When dried in the frozen state the virus retains its vitality for as long as seven and a half years.

An important advance was made by Theiler (1930) who showed that white mice can be infected with yellow-fever virus by intracerebral inoculation; the mice develop a fatal meningo-encephalitis. After a certain number of passages in mouse brains, it becomes established as a neurotropic virus, which no longer reproduces yellow fever of the usual type when monkeys are injected subcutaneously with the brain tissues of infected mice. Infection of rhesus monkeys can be produced by subcutaneous or intraperitoneal injection of infected blood or tissues or by smearing yellow fever blood on the unbroken skin; the virus may also be absorbed by the mucous membrane of the alimentary tract. Rhesus monkeys artificially infected with this virus usually die from four to seven days after inoculation, before they have had time to develop immune bodies.

Nature of Viruses.—Viruses occupy the border-line between the living and non-living. They are ultramicroscopic and it means that they are less than

0.2 micron and can only multiply and reproduce inside susceptible living cells. They are widely spread amongst bacteria, plants, insects and animals. There are about 60 of these viruses which affect man. The fact that they can be visualized with the electron microscope and grown in the laboratory has given a great impetus to their study. The two principal methods now are tissue culture and hens' eggs.

On entry into a cell there is an "eclipse period" when the virus cannot be demonstrated. It breaks up and merges with the substance of the host cell, but it does not lose its identity, because on emergence it has all its original properties. It has been shown in the case of phages that each particle is provided with a head and a tail. The former contains nucleo-protein; while the outer shell of the head and the tail consist of phosphorus-free protein. The nucleo-protein is the essential part and responsible for its genetic continuity. A phage attaches itself to a bacterium by means of its tail and then infects the nucleo-protein molecule. Inside the bacterium the nucleo-protein multiplies at its expense, and, before leaving, it surrounds itself with its shell-tail outfit to complete its existence and renders it capable of infecting other bacteria. It is on this account that it is so difficult to destroy viruses by chemotherapy. At the stage of preliminary infection the individual feels well and it is only when the virus is lodged within the cells that symptoms become recognizable.

"Interferon" (Isaacs, 1958) is a substance which has been elaborated at the Institute for Medical Research and which holds out great possibilities. When inactive influenza virus is mixed with chick chorio-allantoic membrane a substance is produced which has the property of interfering with the growth of viruses and to which the name of "interferon" is given. It has now been obtained from other viruses and it is produced whenever "virus interference" is established and it is active against a wide range. It is of no use to the virus, but when incorporated into its system it is unable to make use of the hypothetical intermediary and it dies. It blocks an essential step in the growth of the virus.

The virus is so virulent that infection of monkeys may occur from the bite of a single infected *Aedes aegypti*. The species of monkey susceptible to the pantropic or viscerotropic strains are the rhesus monkey (*Macaca mulatta*), the crab-eating macaque (*M. irus*), the brown macaque (*M. fuscata*) and also, to a lesser degree, *M. sinicus*. The Barbary ape from North Africa (*M. sylvana*) is also susceptible. Amongst New World monkeys, marmosets usually die, while some species of capuchin monkey recover after a febrile attack. Guinea-pigs are completely refractory, so that inoculation of these animals with blood from a suspected case serves, negatively, as a means of differentiation from *Leptospira icterohaemorrhagiae*. Guinea-pigs, however, develop immune bodies after inoculation. European hedgehogs, more especially the Central African species, are very susceptible.

There is great variation amongst laboratory animals to intracerebral inoculation, and none react so constantly as do white mice. Under laboratory conditions African monkeys (*Cercopithecus*) are not necessarily immune to the viscerotropic virus, but they do not react by fever and the virus multiplies and circulates in their blood for a short time. Lambert investigated the state of immunity of forest monkeys in parts of Brazil where there had been a human epidemic in 1935. Immune bodies were found in 10.75 per cent. of 1,666 sera collected from 1,153 monkeys and all except two of the 120 immune animals were adults. In another area, where the human disease occurred in 1945, immune bodies were found in monkeys of all ages. These cebus monkeys have a very limited range and yellow fever is seldom fatal in them. The evidence suggests that the infection is spread by infected mosquitoes in the isolated forest patches in the area. It seems

therefore that in 1945 yellow fever did not spread in monkeys beyond the areas in which this fever was to be found in man.

The virus can enter the skin of man and through the conjunctiva or nasal mucosa under certain circumstances and cause fatal infections, as has occurred during autopsies on yellow fever cases performed without rubber gloves. Laboratory workers have also become infected by examining monkeys after death. A number of isolated cases have occurred amongst laboratory attendants whilst undertaking blood examination of suspected cases, or whilst working with the virus. These infections, which numbered 35, were due to the pantropic and neurotropic strains (Berry and Kitchen) but, since the introduction of an efficient method of immunization, laboratory infections have entirely ceased.

Cultivation of the virus.—The virus of yellow fever can be grown solely in the presence of living cells. Haagen and Theiler first succeeded in culturing the neurotropic strain in a medium of minced chicken embryo suspended in a mixture of normal monkey serum and Tyrode solution. Even after a hundred passages there was no appreciable loss of neurotropic activity. Subsequently Lloyd cultivated the pantropic virus (known as pantropic because it produces lesions in all embryonic layers of susceptible vertebrates) which, after more than one hundred subcultures, had become attenuated and could, on this account, be used for protective vaccine. Later still, Elmendorf and Smith grew the pantropic virus on the chorio-allantoic membrane or in the yolk sac of the developing chick embryo, which is the method now universally employed. Strain D-17 of the Rockefeller Institute is such an attenuated virus.

The neurotropic strain of yellow fever virus.—Once the virus has become fixed for mouse brain it can be passaged indefinitely by intracerebral inoculation in these animals and subsequently, when injected intraperitoneally, it fails to kill. It causes meningo-encephalitis, not only in mice, but also to a lesser degree in guinea-pigs, agoutis, squirrels, peccaries, capybaras, coatis and field voles, as well as all species of monkey, and as a rule, viscerotropic lesions are not produced.

Physical properties of the virus.—The virus, both neurotropic and viscerotropic, passes readily through ordinary filters, Berkefeld, Chamberland and Seitz. Findlay and Broom, by filtration through graded collodion membranes, have shown that its approximate size is between 18 and 27 μ . Both the viscerotropic and neurotropic strains of virus are inactivated at a temperature of 60° to 65° C. When dried and frozen, the virus can retain its vitality for many years.

Protection tests as an index of endemicity.—The fact that, after an attack of yellow fever, immune bodies are present in the serum for the remainder of the patient's life, and that, when a mixture of immune serum and yellow fever virus is injected into susceptible animals, infection does not take place, suggested the practical application of "protection tests" for the diagnosis of recovered cases of yellow fever. When a mixture of the pantropic virus and the serum under examination is injected into a rhesus monkey, if the serum contains immune bodies, the animal does not die. This is known as the "monkey-protection test."

When, however, the neurotropic virus is employed, a mixture of the serum and infected mouse brain is injected intraperitoneally into mice which are simultaneously inoculated intracerebrally with starch. If the serum contains immune bodies encephalitis does not ensue. This is known as the "mouse-protection test." Both tests possess a high degree of specificity, and results obtained by the two in the same areas of Africa and South America are in close agreement. The mouse protection test is now universally employed and has recently been simplified by modifications introduced by Whitman (1943). This is based on the greater susceptibility of immature white mice to extraneural injection of yellow fever virus. In mice between 18 to 21 days the degree of susceptibility is such that uniform death may be produced by injecting one tenth of the virus

dosage required for adult mice without the need for *intracerebral* injection of starch. In these immature mice, when two parts of immune serum are added to one part of virus, the results of injecting 0.06 ml. of the mixture are equivalent to injecting adult mice, which have received intracerebral starch, with 0.6 ml. This obviously permits satisfactory tests to be made on much smaller serum samples than those required for standard tests.

The technique is as follows. Mice are injected with filtrates of 10 per cent. mouse brain virus. Three days later the brains are removed and emulsified in 15–20 per cent. suspension in saline and subsequently centrifuged at high speed for 40 minutes. The sera to be tested are measured into tubes in quantities of 0.4 ml. each; 0.2 ml. of virus is inserted into each tube of test sera and immune controls.

By this test it has been found that, both in Africa and South America, the areas which have been infected with yellow fever during the lifetime of the present generation are much more extensive than had been previously imagined. Despite the non-recognition of outbreaks of clinical yellow fever in native populations, it has been found in Northern Nigeria, for instance, that 30.4 per cent. of sera are positive. Somewhat similar results have been obtained from French West Africa and the Southern Sudan. There is some evidence that the immune bodies may pass from mother to child by the placenta and also by the milk. In Africa mothers commonly suckle their young for two or three years; this may explain why yellow fever in children is asymptomatic, the children being bitten by an infected mosquito, while their blood contains immune bodies. Monkeys born of immune mothers possess immune bodies in their serum at birth.

Porterfield (1956) has applied the hæmagglutination test to the diagnosis of yellow fever and has obtained close agreement between it and the mouse-protection test.

Transmission of the virus through the mosquito.—The virus multiplies in the insect vector during a variable extrinsic period. During this period the mosquito is not capable of transmitting the virus by its bite. In *Aedes ægypti* it ranges from 4 days at 98.6° F. (37° C.) and 12 days at 78.8° F. (26° C.) to 18 days at 69.8° F. (21° C.). Under natural conditions the percentage of mosquitoes becoming infected is small. Possibly this may be explained by the small quantity of blood (0.01 ml.) imbibed by *Aedes ægypti*. There is no proof that the virus is hereditarily transmitted through the mosquito.

At 10–18° C. the virus can persist in the insect's body for a long time without being capable of transmission, but at 28° C. for one week this becomes possible. At 37° C. this can occur in four days (Davis). In the S. American species¹, *Hæmagogus spegazzinii falco*, the extrinsic incubation period is markedly affected by temperature. This indicates that as the mosquito is placed in a progressively less favourable environment it becomes less suitable for the virus. Serial passage of virus strains through mouse brains or chick embryo results in a type poorly adapted for development in mosquitoes. When the virus content of the blood-stream of an infected animal is 100 M.D. for mice per 0.03 ml. it is unusual for a single mosquito to become infected, but as the virus content of the blood rises beyond 10,000 M.D., the percentage of infected mosquitoes rises rapidly. It is amongst those insects which breed in tree holes that the bulk of yellow fever vectors are found. There is evidence that immune serum can neutralize virus in the stomach of the mosquito. The mosquito is the reservoir host of the virus.

It has been shown that *A. ægypti* in Brazil has a flying range of 120 metres. By using radioactive phosphorus and strontium for marking mosquitoes, Burgher and Taylor were able to show that they are distributed largely by wind drift

¹ The commonest species *H. spegazzinii* can only be distinguished from the other proven vector of yellow fever—*H. capricornis*—by the male genitalia.

rather than by their own flight. *A. ægypti*, which is a domestic species in S. America and W. Africa, in the Bwamba country area in Uganda is quite different in life habits, so that it is virtually incapable of aiding in the spread of yellow fever. *A. africanus* can transmit yellow fever in nature. *A. simpsoni*, which has a wide distribution throughout Africa, behaves differently in Bwamba country where it breeds in plant axils, especially bananas and colocasia. In forest areas it replaces *A. ægypti* as vector of yellow fever virus. *Tæniorhynchus africanus* is the commonest arboreal mosquito in forest canopy, but there is no actual evidence that it transmits yellow fever in nature.

In S. America mosquitoes of genus *Hæmagogus* and *Aedes leucocelænus* have a pattern of daytime feeding which brings them into contact with man as well as with monkeys.

Observations on the habits of *A. ægypti* indicate that the female does not lay eggs until she has fed on blood, and that these are deposited three days after feeding. At this stage she is especially susceptible to infection with the yellow fever virus (*see also* p. 321). It has been shown that the virus undergoes multiplication in the mosquito and that it is present in its alimentary canal for at least ten days after an infective meal. Subsequently, it becomes centred in the salivary glands. It has been shown that *A. ægypti* has now largely disappeared from Central America so that, in spite of jungle yellow fever, no urban cases have occurred for many years.

Species of mosquito, other than A. ægypti, capable of transmitting the virus.
—In South America jungle yellow fever occurs in the absence of *A. ægypti*. Other species have been found infected: *Aedes leucocelænus*, *Hæmagogus spegazzinii falco* and some *sabethinæ*. In Bwamba, Uganda, *Aedes simpsoni* has been proved to be the vector of jungle yellow fever. Another species, *A. africanus* bites at night and feeds on monkeys at 80 ft. above the ground. The jungle species of mosquito vectors are usually inhabitants of the tree tops and rarely descend to ground level, and it has been shown that some infected *Hæmagogus* have never been in contact with man at all.

The following have been found capable of transmitting yellow fever virus by bite under laboratory conditions, but probably not all do so naturally:—

South American mosquitoes: *Aedes ægypti*, *A. fluviatilis*, *A. leucocelænus*, *A. scapularis*, *Hæmagogus capricornii*, *H. spegazzinii* (*H. s. falco*), *H. equinus*, *H. splendens*, transmit virus.

The following are susceptible: *Aedes nubilus*, *A. serratus*, *A. terrens*, *A. fulvithorax*, *A. tæniorhynchus*, *Hæmagogus urartei*, *H. tropicalis*, *Psorophora ferox*, *P. cingulata*, *Tæniorhynchus albicosta*, *T. chrysnotum*, *T. fasciolata*, *T. justamansonia*, *T. titillans*, *Wyeomyia bromeliarum*, *Culex fatigans*, *C. nigripalpis*.

A. leucocelænus is widespread and plays an important part in the spread of yellow fever. *Hæmagogus* are tree-hole breeders and feed on marmosets. Yellow fever virus is isolated from the genus *Sabethoides*, which are difficult to keep in laboratory. *Trichoprosopon frontosus* is a species belonging to the genus *Gældia*, a sabethine, which can transmit in laboratory and is widespread.

African mosquitoes in the laboratory: *Aedes ægypti*, *A. africanus*, *A. luteocephalus*, *A. metallicus*, *A. simpsoni*, *A. vittatus*, *A. stokesi* (*apiocannulatus*), *A. taylори*, *Eretmapodites chrysogaster*, *Culex thalassius*.

The following are susceptible: *Tæniorhynchus uniformis*, *Aedes cummingsi*, *A. irritans*, *A. nigricephalus*, *A. lineatopennis*, *A. punctocostalis*, *A. strelitæ*, recently described from Natal.

Mattingly found in S. Nigeria, as in Uganda, that *Aedes africanus* bites mainly at tree-top level and in the evening twilight. This mosquito was first implicated by Haddow and colleagues in the forest cycle of yellow fever in Uganda. The virus was obtained from a batch caught in nature. Monkeys were exposed on platforms at canopy level in the forest; only one out of 39 became infected.

Pathology.—The pathological appearances vary very greatly with the clinical course of the disease. In typical cases the olive-yellow colour of the skin is most marked in the dependent parts of the cadaver, especially in parts subjected to pressure. Rigor mortis is pronounced. Petechiæ are common in the skin and serous membranes; more considerable extravasations of blood may be found in the muscles. The brain and meninges are hyperæmic and may be studded with minute effusions; like the other tissues of the body, they may be stained a lighter or deeper yellow. The cartilages are intensely yellow. Intensive hæmorrhagic lesions have been observed in the lungs in 90 per cent. of cases (Klotz and Belt).

The blood in the vessels of the general circulation is not firmly coagulated. An important fact, explaining the liability to passive hæmorrhages, is the existence of a generalized fatty degeneration of the capillaries and smaller blood-vessels. The stomach usually contains black or fluid blood. The folds of the gastric mucous membrane are swollen and there are arborescent patches of ecchymosis. The small intestine contains a dark material similar to that in the stomach. Only after microscopic examination of the organs, especially the liver, can a pathological diagnosis of yellow fever be made.

The virus of yellow fever, like certain other viruses, has a particularly destructive action on the liver cells, and by microscopic examination of liver sections alone it is usually possible to arrive at a diagnosis. The liver is of a yellowish colour and is compared to box wood. Necrobiosis and acidophilic necrosis are found in the mid-zonal region of the liver lobules, to a lesser extent at the periphery. Fatty changes are more extensive than the necrosis. The liver cells are often separated one from another and tend to assume a rounded shape; fatty degeneration may be very intense (Fig. 62). The typical lesion is a coagulative necrosis with a marked edge, surrounded by a narrow clear halo. Frequently the cytoplasm, in whole or in part, undergoes a hyaline degeneration—hyaline coagulation necrosis—together with hyaline bodies, first described by Councilman, while the cytoplasm of all the liver cells stains more intensely with acid stains such as eosin. The necrosis of the liver is not exactly a *midzonal necrosis*, as is often stated, but a scattered necrosis occurring throughout the lobule, giving a salt and pepper appearance in sections stained with hæmatoxylin and eosin. The nuclei of the liver cells exhibit

margination of the chromatin round the nuclear membrane, while in some cells the nucleoplasm is occupied by acidophilic intranuclear masses (Fig. 63). Hyperplasia of the Kupffer cells is usually noted. Usually only a small number is affected, but with certain strains 70-80 per cent. exhibit inclusions. In the rhesus monkey a high percentage of cells always shows intranuclear inclusions.

Definite changes are found in the kidneys. The reaction is a *nephrosis*, not a *nephritis*. Hæmorrhagic foci under the capsule and in the cortex are common. Fatty changes with necrobiosis and necrosis of the tubular epithelium are present. The tubules, here and there, are filled with casts, either of an albuminoid material or of débris of desquamated epithelium.



Fig. 62.—Yellow fever : section of liver (low power) showing fatty and hyaline degeneration and Councilman lesions. (Dr. G. M. Findlay.)

corresponding with the casts in the albuminous urine. Granular and hyaline casts are found throughout the tubules of both cortex and medulla, Hoffman regarded lime-casts in the convoluted tubules as distinctive of yellow fever.

Symptoms.—There is the same variety in the initial symptoms of yellow fever as in other specific fevers. In both urban and jungle yellow fever many mild and clinically unrecognizable cases occur. In the first stage the symptoms may range from an almost imperceptible febrile reaction to severe prostration. Yellow fever in man may be divided into (1) the very mild, (2) mild, (3) moderately severe, and (4) malignant types. In very mild yellow fever the only symptoms are fever and headache which last

from a few days to a day or two. This febricula is undiagnosable, even in an epidemic, for unapparent infections occur, especially in endemic areas, as a result of long contact with the virus. Some infections are found in babies who are losing the passive immunity bestowed upon them by their immune mothers. The *incubation period* is from 3-6 days though considerably longer periods are recorded in accidental infections in which it is from 10-18 days.

Roughly speaking, and provided there are no complications, an attack of yellow fever is divisible into three stages—(1) the initial fever; (2) the “period of calm”; and (3), in severe cases, the period of reaction.

The initial fever is usually sudden in onset, and lasts from three to four days. The maximum temperature is generally attained within the first twenty-four hours, or by the second day, and, in a case of medium severity

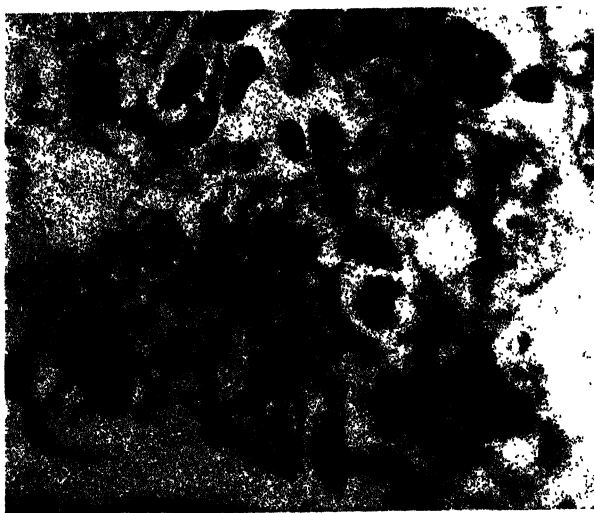


Fig. 63.—Yellow fever: section of liver $\times 2,000$ showing acidophilic intranuclear inclusions (Torres bodies). (Dr. G. M. Findlay.)

may rise to about 108° or 104° F. During the three or four succeeding days the mercury slowly sinks to 98° or 99° F., the daily fluctuations being seldom more than a half to one degree. It occasionally happens that high temperature is maintained for more than three days, and also that the maximum is not attained until the eighth, but, as a rule, it is reached within two days of the onset (Chart 19).

With, or soon after the initial chill or rigor, severe headache sets in and is generally a prominent feature. For the most part the pain is concentrated about the forehead, in the circumorbital region and in the eyeballs. In many cases it is associated with intolerance of light.

Loin pain is another very distressing symptom; it may amount to positive agony; the backache may be as bad as in a severe case of small-

pox. The legs, too, ache excessively—particularly the calves, knees, and ankles; they feel as if broken. Epigastric pain is generally prominent.

The face is flushed and swollen; the eyes are shining, injected, and ferrety; the skin is dry.

What with pains and febrile distress, the patient passes into a very miserable condition. He is restless and continually tossing about.

At first the pulse ranges from 100 to 120, and is full and strong; but as the disease progresses, the pulse loses its sthenic character, gradually falling in force and frequency until, at the "period of calm," it becomes remarkably slow and compressible, beating perhaps only 80 or 40 times per minute. This fact may be of particular value in diagnosis, and is known as *Faget's sign*—that is, a falling pulse-rate with a constant temperature, or a constant pulse-rate with a rising temperature. It is in fact

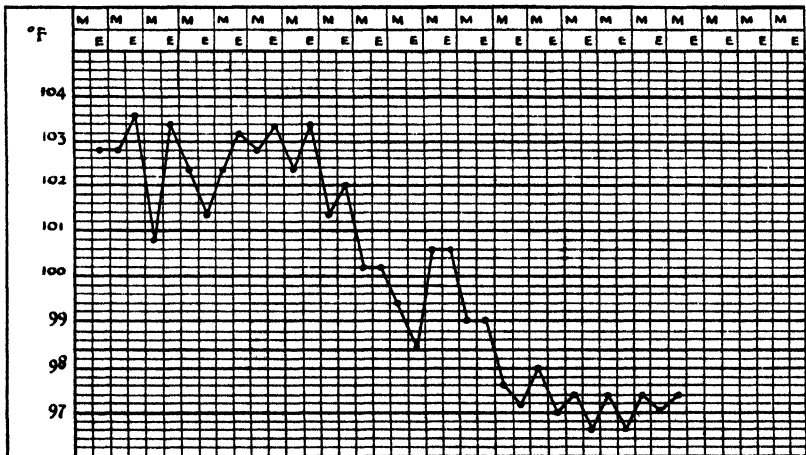


Chart 19.—Laboratory infection of yellow fever. Recovery.

a sign which emphasizes the lack of correlation of temperature and pulse, so that by the second day, notwithstanding the high temperature, the pulse-rate becomes slower, and by the third or fourth day it has probably decreased 20–40 beats from its initial rate. As a prognostic sign—a quickening pulse rate with a falling temperature indicate that death is near.

At the outset the tongue is not very dirty, but it soon acquires a white coating on the dorsum, the edges remaining clean. It is not so swollen and flabby as in malarial fever; on the contrary, it is rather small and pointed throughout the disease. This is regarded as an important diagnostic mark; taken along with the progressive diminution in the strength and frequency of the pulse and the peculiar behaviour of the temperature, it is nearly conclusive of yellow fever. Later, the tongue dries and, at the same time, thirst becomes intolerable. The palate is congested and swollen; the gums may also swell and bleed.

The congested appearance of the face at the onset of the disease tends to subside ; so that by the time the asthenic stage is reached the features may have become small, the eyes sunken, and the eyelids discoloured by ecchymoses.

In some cases the skin is hot and dry throughout ; in others it may be bedewed with perspiration from time to time ; or the sweating may be constant, especially if collapse sets in.

By the third day the scleræ assume a yellowish tinge, and very often the skin acquires that yellow colour from which the disease derives its name. In severe cases bluish spots may be observed and are due to subcutaneous hæmorrhagic effusions. It must not be understood, however, that every case presents this colour of skin ; in some it is entirely absent, but if carefully looked for there is always some yellowness of the scleræ. The yellow tinging of the skin generally shows about the end of the first stage, deepening in intensity as the case advances, and remaining apparent for a considerable time after convalescence has become established. It ranges in depth from a light saffron to a deep mahogany brown. In fatal cases it is always present—not necessarily during life, but invariably after death. The skin in bad cases is said to emit a peculiar odour like gun-washings, or, as Jackson puts it, like the smell of a fish-market.

Petechial, erythematous, papular, and other eruptions may show themselves in different cases ; but in yellow fever there is no characteristic eruption, unless it be an erythematous congestion of scrotum or vulva, which occurs in a proportion of cases and is described as diagnostic.

An important feature, from the diagnostic as well as from the prognostic point of view, is the appearance, in some cases almost from the outset, of albumin in the urine, together with a tendency to suppression. During the stage of depression, the urine may fall to a few ounces, and be loaded with albumin to the extent of one-half or even two-thirds (usually about 2 grm. of albumin per litre). The more pronounced these symptoms, the graver the prognosis. The amount of albumin increases as the temperature falls. Urea (even during the incubation period) and uric acid are very much diminished, the former in severe cases falling to 1.5 grm. to the litre. The urine is almost invariably acid, depositing granular casts, and sometimes giving spectroscopic evidence of hæmoglobin. Bile-pigments and bile-stained tube-casts show themselves towards the end of the disease, usually about the fifth day, and their appearance is regarded as a favourable omen. Peptonuria indicates a serious prognosis. The blood urea is usually high during the terminal stages. A well-marked *tache* is present on the forehead, as well as on other parts of the body.

At the outset the bowels are confined. In the second stage, diarrhœa, perhaps of black material resembling the vomit, may supervene ; or there may be actual hæmorrhage of bright-red blood from the bowel.

Nausea and vomiting are more common than in other fevers. The well-known *black vomit*—always a grave symptom, but fortunately not by any means an invariable one—forms one of the most striking features of this disease. In the earlier stages of the fever, vomiting of bilious matter is common. This may subside or, after a time, give place to “ coffee-grounds ” which seem to gush up without straining or effort on the patient’s part,

and which gradually deepen in colour until they become uniformly black. On microscopical examination the vomited material is found to consist of broken-down blood-corpuscles and altered hæmoglobin suspended in a yellowish mucoid fluid. This material is, doubtless, in the main derived from blood transuded through the walls of the capillaries of the mucous membrane of the stomach. It is intensely acid. Though the black vomit may not always be seen in fatal cases during life, the material is invariably found in the stomach *post mortem*.

Sometimes pure blood is thrown up from the stomach; similar passive hæmorrhages may take place from almost any part of the body—from eyes, ears, nose, mouth, bladder, uterus and so on. "Everything is congested at the outset, everything bleeds at the end," is a well-known adage.

Death may occur during the early acute stage, being preceded by a rapid rise of temperature. The majority of deaths occur on the fifth and sixth days; the end seldom comes before the third or after the eleventh day, and, at this stage, is generally preceded by a rapid fall of temperature.

In mild cases the "period of calm," which sets in after the subsidence of the initial fever, may last for several days before convalescence. The most constant symptoms are headache, pain in the back and extremities, photophobia, anorexia, prostration, congestion of the eyes, with a typical tongue, pointed and coated, but with red edges and tip. In other instances the secondary fever terminates in a crisis of sweating and prolonged convalescence.

Even in Europeans, as illustrated by certain of the infections contracted in the laboratory, yellow fever may be comparatively mild and may resemble an attack of influenza.

Relapses are unknown. The immunity produced by one attack of yellow fever is usually permanent, as permanent as that produced by smallpox or measles.

As a rule there is no anæmia, but there is a slight leucocytosis early in the disease, soon followed by a leucopenia, which reaches its lowest point about the fifth or sixth day (Berry and Kitchen); the polymorphonuclear leucocytes are not increased, but there is an increase of mononuclear cells during convalescence. In human infections the virus has been shown to exist in the blood 107 hours after the onset of fever, while antibody has been detected after 88 hours, thus confirming what had already been suspected on epidemiological grounds of the simultaneous presence of virus and antibody in human blood in yellow fever. In icteric cases the Van den Bergh reaction is biphasic.

The overall fatality rate in yellow fever lies between 5–10 per cent. of all cases, but this rate may rise above these limits in a given epidemic.

Complications and sequelæ.—Suppurative parotitis (usually unilateral) is the most striking complication, but lobar pneumonia is more serious and myocardial failure after apparent complete recovery constitutes a definite hazard.

Experimental yellow fever infection in monkeys leads to a febrile reaction which is not high during the early days of the illness, but subsequently there is a sudden rise of temperature followed by a rapid fall and the animal dies in coma.

In some there is an alternating rise and fall and in others a rapid crisis and death. Death may take place as early as the fourth or as late as the fifteenth day.

Diagnosis and differential diagnosis.—Routine urine examination must be carried out in all febrile cases and all with a greater degree of albuminuria than is justified by the degree of fever should be considered suspect. Other points to be considered are the severity of initial symptoms, the relation of pulse and temperature at different stages of the disease, the degree and colour of the jaundice, the time of the appearance and the occurrence of hæmorrhages. Severe yellow fever may be confused with *remittent subtertian malaria*, Weil's disease, *infective hepatitis*, relapsing fever, and *blackwater fever*. The difficulties of clinical diagnosis are often great, especially early in an epidemic. When several deaths, preceded by fever and black vomit, have occurred within a limited area and in quick succession, a suspicion of yellow fever should be entertained, though sometimes this has been observed in Weil's disease and in relapsing fever as well as in outbreaks of infective hepatitis. There is no clinical feature, so far as is known, which would distinguish a mild attack of yellow fever from an ordinary febricula, nor any pathognomonic clinical sign that would absolutely distinguish a malarial remittent from yellow fever and from Weil's disease, though in the latter there is usually a polymorphonuclear leucocytosis. *Dengue* is probably one of the most difficult diseases to differentiate from mild yellow fever. The facies, orbital pains, and backache are similar to those of dengue, but the appearance of the characteristic eruption of the latter disease on the fourth day should settle the diagnosis in any doubtful isolated case. Probabilities must be weighed in diagnosis when it is based on clinical grounds alone. The only reliable guides, as between malarial and yellow fever, are the discovery of the malaria parasite, the characteristic pigment and leucocytic variation in the one, and the determination of their absence in the other, but in an area where malaria is endemic, the finding of parasites does not rule out concomitant yellow fever. *Post mortem*, the presence of pigment in the viscera in malaria, and of extensive necrosis of the liver-cells in yellow fever, is diagnostic. Biopsy of liver tissue by the *Viscerotome* is of value in doubtful cases. Occasionally the two diseases may co-exist. The presence of albuminuria is of value in early and abortive cases, especially in Europeans, but albuminuria is more easily provoked in West Africans from any cause.

In addition to the diseases mentioned, there is great difficulty clinically in diagnosing yellow fever from Rift Valley fever, or, in its milder manifestations, from some forms of influenza, especially of a virulent strain. Occasionally relapsing fever may assume a malignant form with intense icterus and resemble yellow fever in its clinical manifestations, but it may be distinguished by leucocytosis, splenomegaly and spirochætes in the blood. Smallpox, in the first three days, before the rash, may be very similar to yellow fever.

It must also be remembered that in adults infective hepatitis may occur in severe form, while unexplained outbreaks of fever and jaundice, not due to the yellow-fever virus, have been described (see p. 887). In epidemics

of infective hepatitis the jaundice is usually deeper than in yellow fever and the patient may be afebrile.

Laboratory diagnosis.—The virus may be isolated from the blood in the early stages, preferably during the first three days. A venule type of vacuum syringe should be used. The specimen should be kept cool, but never frozen; and the serum which should contain no hæmoglobin, must be inoculated subcutaneously into a non-immune monkey or intracerebrally into white mice of a susceptible strain. The development of specific antibody to yellow fever in the serum can be demonstrated by the mouse protection test.

In fatal cases yellow fever may be diagnosed *post mortem* from a histological examination of the liver, the essential features being the fatty degeneration, mid-zonal necrosis, infiltration with mononuclear cells, and the presence of Councilman lesions (hyaline bodies) and acidophilic intranuclear inclusions.

In any outbreak of febrile illness with jaundice in an area, where the mosquito fauna would permit yellow fever to spread, it is important that serum from patients in the early stages of the disease and from the same patients when convalescent should be examined for yellow fever protective bodies, and liver tissue of cadavers for the appearances typical of yellow fever. By these means, in countries hitherto not invaded by yellow fever, early information may be gained and steps can be taken to control the disease.

Trejos and Romero in Costa Rica (1955), in a series of 86 cases, have shown that in the estimation of plasma prothrombin there is a definite relationship to the severity of the illness. In 24 fatalities the average determination was 20–25 per cent., whereas in those who recovered it was 66·7 per cent. Percentages below 25 were encountered only in cases with an eventual fatal termination.

Prognosis and mortality.—Prolonged initial rigors, algidity, convulsions, suppression of urine, coma and hæmorrhages are all unfavourable symptoms. The prognosis is good if the temperature during the initial fever does not exceed 103° to 105° F. It is better for women (although, if pregnant, abortion is almost invariable) and children than for men; better for old residents than for newcomers; worst of all for the intemperate. Among the permanent inhabitants of the endemic districts the case-mortality is very much lower—7 to 10 per cent. In the outbreak in the Sudan it was about that figure. During epidemics, abortive and ambulatory cases occur; in these, icterus and other characteristic symptoms are often absent. Such cases may be hard to diagnose from febricula or mild malarial attacks, and the mortality is nil. Some epidemics are particularly mild: in others, the majority of the patients die. In the same epidemic the cases may vary in severity from time to time. In children the mortality is low.

TREATMENT

Formerly a much more active treatment than that in vogue at the present day was the fashion for yellow fever. It is now recognized that, as with most virus diseases, the treatment is more a matter of nursing than of drugs. Once in bed, the patient should not be allowed to get up. As in other virus diseases the injection of immune serum is valueless once the infection has begun; given during the incubation period, however, it may prevent, or at any rate decrease, the severity of the disease. Since the virus is efficiently neutralized by the formation of immune serum by

the third or fourth day after the onset of fever, it follows that death is caused by the destructive effect of metabolic toxins on the liver, heart and kidneys.

Experience has shown that a smart purgative at the very onset of the disease may be beneficial. With many, castor oil is the favourite drug, but to be of service it has to be given in very large doses—2 oz. or more. Others use calomel or a saline purge.

Vomiting may be treated with ice pills, or with small doses of cocaine. Luminal is indicated to induce sleep in restless cases, and codeine sulphate to relieve headache and backache. For black vomit, frequent doses of perchloride of iron, ergotine injections and acetate of lead have been recommended. Calcium lactate, in large and repeated doses by mouth, is probably of value in counteracting the excess of guanidine in the blood. The administration of glucose in the treatment of the hepatic conditions represents a distinct advance, and good results from this line of therapy have been reported. Glucose should be given in drachm doses, whenever feasible or, when nausea is present, in 5 per cent. solution intravenously (10 oz.), while injections of 5 units of insulin improve its assimilation. For restlessness, phenacetin or antipyrin is used. When the skin is dry, the urine scanty, and the loins ache excessively, Sternberg recommended pilocarpine.

The feeding is important. So long as there is fever the patient has no appetite; during this time—that is, for the first two or three days—he is better without food. When the fever subsides appetite may return, and a craving for nourishment becomes more or less urgent; the greatest care, however, must be exercised about gratifying this untimely appetite. Protein in the diet is of value in protecting the liver from damage. Gradually the quantities may be increased; but, even when convalescence is established, solid food must be taken very sparingly, and must be of the simplest and most digestible kind. Indiscretion in eating is a fruitful cause of relapse in yellow fever, which may be exceedingly dangerous. Nutrition may be aided by nutrient enemata. Any slight exertion which may cause a rise in blood-pressure may be fatal. It is possible, too, that stimulation of the circulation incident to the taking of food explains the dangers of altering food during the early stages.

Any suspected case of yellow fever should be nursed under a mosquito-net day and night, and preferably in a mosquito-proof room.

Prophylaxis.—A period of six days' quarantine is now accepted by the international sanitary convention as necessary after exposure to infection. It is the duty of sanitary authorities in tropical countries to free the areas over which they have charge from *Aedes ægypti* mosquitoes as far as possible. Although complete destruction is not to be expected, relative extermination of mosquitoes is worth attempting, and certainly can be attained by the vigorous use of the now well-known measures. In Havana, by such means, in a very few months the number of mosquitoes was reduced by 90 per cent., with a corresponding gain to the community in the diminution of mosquito-conveyed disease. The same has happened in Panama, Rio de Janeiro and elsewhere in S. America by residual DDT spraying.

All water-tanks, gutters, and cisterns must be effectually screened against *Aedes aegypti* by fine-meshed metallic gauze; discarded tins should be collected and rolled out by steam rollers; all puddles and stagnant water must be abolished and all holes in trees should be closed or the trees felled. Roof gutters are best abolished altogether. In Africa special attention must be paid to the control of mosquito-breeding on native dhows. Portable fog generators for mosquito control in West Africa are now under trial. The well-known Todd insecticidal generator (T.I.F.A.) apparatus is too heavy and cumbersome for use in rural districts. The "swing fog" machine is the most practical. It is a portable fog generator operating on the pulse-jet principle. A series of fuel plus air charges fired into combustion chambers produce pressure waves along the exhaust pipe. The insecticide is injected into this pipe and vaporized to give a fog. After the apparatus has been started by means of a 6 volt battery, the operation is self-perpetuating, the only moving parts being two flexible valves regulating air intake. The machine weighs 35 lb. when full and runs for $\frac{3}{4}$ hour on its quart fuel tank during which period the seven pint insecticide tank will be emptied 3 or 4 times. For other insecticidal sprays and the use of DDT in combating yellow fever (see p. 857).

Any delay in recognizing the earliest cases of a threatened epidemic is, as shown by experience in New Orleans, most dangerous, leading, as it may, to the rapid multiplication of infected centres.

Ships should not be allowed to clear from infected ports, nor to enter non-infected ports, during the hot season, without adequate inspection.

Aircraft.—It is necessary, in view of the increasing facilities of air travel, to immunize all those proceeding from an endemic to a non-endemic area. It has been recommended by International authorities that measures for preventing spread by aerial traffic should be taken primarily before departure from areas where the disease exists, and only secondarily at ports of arrival. Measures to be taken before departure include freedom of crews and passengers from any risk of infection during six days before embarkation and freedom of aircraft and cargo from the possibility of conveying mosquitoes. It is recommended that the International Civil Aviation organization should take sanitary control of all airfields which might be involved in the spread of disease, control disinsectization of aircraft, control the storage, testing and injection of yellow fever vaccine and control the issue of yellow fever inoculation certificates. Several considerations should modify the tendency to alarmist views of the danger of importing the yellow-fever virus to Eastern countries, such as India or China, where the disease is so far unknown, but where climatic and hygienic conditions are favourable to its spread. One of these is the ease with which aerodromes can be kept free from yellow-fever mosquitoes, as well as the ease and rapidity with which aircraft can be freed.

In the United States it has been proved conclusively that *Aedes aegypti* can be carried by aircraft for long distances, and the necessity of destroying these insects is insisted upon in all aeroplanes flying in tropical countries. Aircraft should be sprayed on the ground prior to departure. Disinsectization is best carried out by dispersing the insecticide in a low-boiling solvent. "Freon" (Freon = dichlorodifluoromethane and a refrigerating agent) is

a low-boiling solvent. Little equipment is needed for the production of aerosols by this method, but the container must have a liquid delivery tube extending to the bottom, since the solution, not the gas, is to be sprayed. Only a small orifice is used so that no expansion takes place until the solution is sprayed into the atmosphere. Aerosols produced by this method are much more finely divided than the mists produced by most spraying methods and settle more slowly. Disinsectization can be effectively carried out in 5-10 minutes.

An aircraft should be regarded as infected with yellow fever, if there is on board any person who within ten days of arrival has been in a yellow fever infected area, and who has not been inoculated against yellow fever for more than ten days prior to arrival.

If a person has alighted from a yellow fever area at a non-infected aerodrome and is in possession of a certificate from the Health Office of that aerodrome stating that, during his stay, he either remained within the non-infected aerodrome, or, if he went outside it, he did so under such protected conditions as would make it impossible for him to be bitten by mosquitoes, he may be permitted to proceed; more especially if he has been protected against the disease by a previous attack or by satisfactory inoculation.

The rules of the International Sanitary Convention must be consulted.

Prophylactic inoculation has been practised since 1931 in West Africa, Brazil, Colombia and South America generally.

Reaction immediately following inoculation with the attenuated paratropic virus is either lacking or consists of slight headache for forty-eight hours. After immunization, immune bodies appear in the serum from the twelfth to fourteenth day, and reach their maximum about the twenty-first. In many immune bodies are detectable for seven years or longer by the mouse-protection test. It is advisable that the blood of immunized persons should be tested every two or three years and, if necessary, they should be re-inoculated. 17 D virus (Asibi strain) is distinguished by marked attenuation. When inoculated intracerebrally into rhesus monkeys it causes encephalitis—which is not usually fatal.

The more viscerotropic the strain the higher is the concentration of the virus in the liver.

A valid inoculation certificate is one certifying that the bearer has been inoculated for the first time more than ten days and less than six years previously to entering the endemic zone, or that he has recovered from an attack of yellow fever and his blood contains immune bodies.

On the whole, results have been very satisfactory. Very few deaths from yellow fever have been recorded in inoculated individuals, though not all are equally protected. *Aedes* mosquitoes are unable to take up the virus from the blood after immunization, so that there is no reason why protective inoculation should not be carried out in areas where these insects are present. Mass inoculation is the only practical answer to the jungle yellow fever problem, as was amply demonstrated by the vaccination of over a million persons in Brazil in 1938. During the second World War nearly a quarter of a million troops in West Africa were immunized by the 17 D virus.

A mild form of meningo-encephalitis in infants inoculated with standard yellow fever vaccine has been reported. The first by Smith (1954) in a five-week-old baby girl. Nervous reaction ushered in by convulsions was noted 11 days after inoculation. The two previous cases reported by Dick and Hogan were associated with primary smallpox vaccination 8 and 18 days previously. Bulging of the anterior fontanelle, pyrexia and rigidity have been recorded with pleocytosis of the C.S.F. In Roodyn's case the child had Jacksonian fits together with facial palsy and deviation of the eyes. G. Stuart (1955) stated that 13 cases had been reported after inoculation with 17 D virus vaccine since August, 1952, seven in France, four in the United Kingdom, one in Portugal and one in Nigeria. It is recommended that in small children under three months great care be taken not to give it in close association with routine smallpox vaccination (until at least 8 weeks have passed).

The yellow fever vaccine, of the requisite standard, has been adopted by W.H.O. (1954). This lays down that the potency must be in accord with the 17 D yellow fever virus vaccine. It is as follows: The finished, dried chick embryo pulp, when rehydrated to its original volume, shall contain no less than 150,000 M.L.N. (mouse units) of virus per ml. of vaccine at the time of passing final potency tests and that, for the satisfactory immunization of man, not less than this amount of M.L.D. of active virus shall be contained in the immunizing dose injected. The Dakar mouse-adapted virus vaccine which is applied by skin scarification, and of which but a fraction of the individual dose thus applied is absorbed by the immunizing dose, has a virus content not less than 5,000 M.L.D. per ml. It is claimed by Courtois (1953) that, by this latter method, immunity can be demonstrated in 96 per cent. of those inoculated after an interval of twelve years. The French in Dakar use a scratch method of inoculating the yellow fever vaccine combined with vaccinia.

Since 1939 in French West Africa inoculation by scarification has been practised and since 1941 it has been made compulsory. The Institut Pasteur at Dakar produces a virus in its 260th passage through mouse brain. It is stored in ampoules as dried cerebral tissue. It is then suspended in gum arabic solution and inoculated by scarification of the upper arm. From 1931 a modification of yellow fever virus has been brought about in 17 D which is a variant of the Asibi strain. The advantages are its attenuated neurotropism for mouse and monkey, as well as attenuated viscerotropism for the latter and its ready cultivation on chick embryo. There are many who think that scarification is more effective than inoculation and it is certainly much more economical. The immunity conveyed lasts 6 years or longer. Eklund (1953) has reported a series of cases of encephalitis in children inoculated with this vaccine and it has been shown that the extraneural inoculation of very small amounts of this virus is more apt to cause encephalitis than do larger amounts.

Other ultramicroscopic viruses resembling yellow fever.—Several of these viruses have been isolated in recent years in North and Central Africa and in South America. The majority are known as Arboviruses and are isolated from tree-top, or canopy, mosquitoes. Arboviruses have antigenic relations which suggest that they have a common ancestor, but there is little concrete information on which to base a coherent scheme of evolution.

Durand's virus (virus D) was isolated in Tunis in 1940 and described by Findlay (1942). It is pathogenic for man as well as the guinea-pig. It is widely distributed in other laboratory animals, and in mice it circulates in the blood without any ill effects. It can be cultured on the chorio-allantoic membrane

of the chick. The particles of this virus are from 38 to 57 μ in size. Whether this virus is widely distributed as a cause of sickness in man, or whether it is mainly confined to guinea-pigs remains to be determined.

Bwamba fever (Western Province of Uganda) has been described by Smithburn, Mahaffy and Paul (1941). This disease is characterized by sudden onset, headache and backache. Symptoms subside in about five to seven days. Nine strains of filterable Bwamba Forest virus were isolated from the blood of as many patients suffering from this illness. It is pathogenic for mice by intracerebral or intranasal inoculation. Guinea-pigs and rabbits are insusceptible. The virus particles are about 113 to 150 μ in size. Another, now generally known as West Nile virus, was found by Smithburn and Jacobs (1942) to be more widely distributed in the West Nile area, in the Bunyoro district. It is also active in the Sudan, Uganda, Kenya and in the Congo. Immune bodies to this virus have been found in the blood of forest monkeys of genera *Cercocebus* and *Colobus*.

E.M.C., or Mengo virus, was described by Dick and others in Uganda in 1948; it causes paralysis in man and monkeys and is related antigenically to an phalomyocarditis virus isolated from rodents. Injected into humans it causes mild pyrexia. In monkeys it causes lesions of the central nervous system as well as of the cardiac muscles. Semliki Forest virus has been found in mosquitoes and causes encephalitis in mice.

Unknown viruses capable of infecting mice when inoculated intracerebrally have been isolated from wild-caught mosquitoes. In Brazil Laemmert and Hughes isolated a virus from *Aedes* and *Psoorophora*, which could be transmitted by *Aedes aegypti* in the laboratory. A somewhat similar virus was isolated from *Aedes abnormalis* by Smithburn and Haddow and is known as Uganda S. Another is known as the Bunyamwera virus, and others as Sindbis, Ntaya, and Zika. This latter when inoculated into a volunteer produced mild pyrexia and headache (Bearcroft, 1956). Altogether eight viruses have been isolated in Uganda.

All these viruses, with the exception of the West Nile virus, have been isolated from mosquitoes. Mengo virus has been isolated from *Taeniorhynchus africanus* and *T. uniformis*; Zika virus from the former; Ntaya from a mixed collection; Bunyamwera from species of *Aedes*; Semliki from *Aedes abnormalis* and Uganda S from *A. longipalpis*. There is good evidence that man becomes infected with Bwamba fever, West Nile virus and Mengo encephalomyelitis; possibly also with Ntaya, Uganda S and Zika. Mengo virus has been isolated from the blood of a mongoose, whilst the isolation of Zika, as well as the former from captive rhesus monkeys, leaves no doubt that they were naturally infected. Only in the case of Bunyamwera virus is there any direct evidence of human infection, when Southam (1951) inoculated four patients with it and produced symptoms (Dick, 1953).

Mayaro virus (Downs) with antibodies in the blood has been isolated (1956) from a number of residents in Trinidad. It has also been found in Brazil, Bolivia and possibly in Uganda. "Salisbury Fever" described by Downs (1956) in children 4-9 may be another such virus.

The following is a list (Smithburn) of viruses believed to be arthropod-borne in Africa and pathogenic to man, other than yellow fever, Rift Valley and sandfly fevers.

Semliki Forest (E. and W. Africa).

Sindbis (Egypt and S. Africa).

Chikungunga—a dengue-like virus (E. and S. Africa).

Middleburg (S. Africa).

A.R. 136 (S. Africa).

West Nile (E. Africa, Egypt).

Ntaya (E. Africa).

Zika (E. and W. Africa).

Uganda S. (E. Africa).

H. 336 (S. Africa).

Spondweni (S. Africa).

Wesselbron (S. Africa).

Bwamba fever (E. Africa).

Pongola (S. Africa).

Bunyamwera (E. and S. Africa).

Simbu (S. Africa).

The factors in the past and future evolution of the Arboviruses have recently been reviewed by Gordon-Smith (1960).

CHAPTER XVIII

RIFT VALLEY FEVER

Synonym. Enzootic hepatitis.

Definition.—An epidemic disease of sheep and cattle in Kenya, caused by a filterable virus which is transmissible under certain circumstances to man. The best account of this disease is by G. M. Findlay (1932). An outbreak in S. Africa of considerable size has been described by Mundel, Gear and others in 1951.

Ætiology.—The virus occurs in the blood and appears to be present in the plasma and attached to the blood-cells; it is found in the blood, liver, spleen, and other internal organs, but not in the urine. It may pass through the placenta of pregnant animals and infect the foetal tissues. The size of the virus particles has been estimated by Broom and Findlay to be between 23 and 35 $m\mu$. When present in plasma, or suspended in physiological saline at pH 7.2, the virus can pass through Berkefeld N.V. and W. candles, as well as through Chamberland L₂ and L₃ candles, without any loss in virulence. Blood preserved in oxalate-carbol-glycerin has retained its virulence for mice when preserved in the ice-chest at 4° C. for eight months. Mackenzie (1933) succeeded in cultivating the virus without loss of titre in a medium of chick embryo and Tyrode's solution. The character of this virus remains unaltered. It can also be grown on the chorioallantoic membrane of the developing chick embryo.

Apart from the susceptibility of sheep, lambs, goats and wild game, especially buck, the pathogenicity of the virus for man and monkeys (*Macaca*) and many small rodents (mice, field-mice, wood-mice, hamsters, dormice, and rats) is noticeable. Mice succumb in two to four days. Cats appear to be slightly susceptible. Indian and South American monkeys of the genera *Macaca*, *Hapale* and *Cebus*, are relatively susceptible, but African monkeys of the genera *Cercopithecus* and *Cercocebus* are relatively insusceptible, and do not suffer from any febrile reaction. Local East African rodents have been found by Daubney and Hudson to be highly susceptible to this virus, and probably play a part in its dissemination. These are *Arvicanthus abyssinicus*, *Mastomys coucha*, and *Rhabdomys pumilio*.

During April and May 1944, Smithburn, Haddow and Gillet obtained the virus from mosquitoes caught in an uninhabited forest area from Mongiro, Bwamba County, in Western Uganda. The mosquitoes involved were *Aedes tarsalis* and *A. albocephalus*, *A. (Stegomyia) de-boeri* subsp. *de-meillon*i and *Eretmapodites* sp., containing *E. chrysogaster*, *E. inornatus*, *E. ferox* and *E. leucopus* subsp. *productus*. The sera of two persons from Bwamba were positive, but that of 72 wild monkeys belonging to 9 species in Bwamba were all negative. As *Eretmapodites* mosquitoes do not occur in Kenya it is thought that the vector there is *A. tarsalis* and *A. dendrophilus*.

Using a mouse-protection test somewhat similar to that used in yellow fever, Findlay, Stefanopoulou and MacCallum have found that immune bodies can be detected in the blood of natives from the Nuba Mountains in southern Anglo-Egyptian Sudan, northern Uganda, and French Equatorial Africa. No immune bodies were found in bloods from West Africa.

Pathology.—The pathological change in animals consists of a focal necrosis of the liver. These foci may be discrete, as in sheep or goats, or may coalesce

so as to involve the whole liver, as in young lambs, and in mice, rats and other rodents. The histological changes consist of an infiltration with mononuclear and polymorphonuclear cells, and a hyaline degeneration of the cytoplasm of the liver cells (Councilman lesions). In the livers of infected mice, acidophilic inclusions (or intranuclear bodies) have been found, by Findlay, as in many other filterable virus diseases, and similar bodies have been described by Daubney and Hudson in the livers of experimentally-infected sheep in Kenya. The nuclear changes in the affected cells are of the type known as "oxychromatic degeneration."

Symptoms.—In those cases which have been observed in man the incubation period varied from four and a half to six days. At the commencement of the fever a feeling of nausea and a sensation of fullness in the hepatic region is experienced, and this is followed by violent headaches, pain in the back, rigors, and general malaise. The face is flushed, and there is photophobia without, however, any marked conjunctival congestion. Retinal complications and loss of vision were serious and not uncommon in the S. African outbreak in 1951 and are said to be distinctive (Freed and Shrire). The tongue is thickly coated and epistaxis usually occurs. Bone pains are confined to the shoulders, back, and legs. The temperature varies between 101° and 102° F. On the fourth day of the fever the temperature falls to normal, accompanied by profuse sweating; a post-febrile weakness and a tendency to sweating on the least exertion remain. The bowels are usually constipated and the urine is deep yellow. There appears to be an initial slight leucocytosis, followed on the third and fourth days by a definite leucopenia, which persists into convalescence.

One human case has been recorded in which the fever lasted for ten days, ranging from 101°–103° F., and showed a regular saddle-back character. The virus of Rift Valley fever thus produces in man a disease resembling in many respects dengue and phlebotomus fevers. In one instance three febrile attacks of decreasing severity were noted. One fatal infection in man was recorded by Schwentker and Rivers (1934) from the Rockefeller Institute, New York. This occurred in one of the members of the staff who had been working with the virus. Although the course of the illness was otherwise typical, it was complicated by thrombo phlebitis—a condition not previously described in association with this disease—and death was due to a pulmonary embolus. In the early stages the virus was present in the patient's blood and was pathogenic to mice. Death occurred on the forty-fifth day of the illness.

Immunity.—An immunity can be established in infected monkeys and it has been shown that they cannot be re-infected with massive doses of the virus for at least six months. In man immunity is present for at least sixteen years.

Diagnosis.—The virus of Rift Valley fever is distinguished from that of yellow fever by its pathogenicity on intraperitoneal injection for small rodents (mice and rats), and by the fact that monkeys (*Macaca*), immune to yellow fever, are later susceptible to infection with the virus of Rift Valley fever. Human cases have also occurred in persons known to have suffered from yellow fever. The serum of recovered cases gives a specific complement-fixation reaction, and contains immune bodies which neutralize the virus when serum and virus are inoculated into mice. There is no relationship with dengue, phlebotomus fever, or West Nile virus.

Treatment.—In human cases, treatment by injection of immune serum has been attempted by Findlay, though it is not possible to estimate the result. In view of the toxic action on the liver, glucose should be given by mouth. The virus is not sensitive to sulphonamides.

Prophylaxis.—Evidently in the midst of a sheep epidemic human beings are themselves very susceptible to infection. There is some evidence to show that in the Naivasha district of Kenya, a mosquito—*Mansonia fuscopennata*—may be responsible for the transmission of the virus, whilst Daubney and Hudson also report that it is possible to convey the disease by inoculation of the body-contents of other mosquitoes, such as *M. versicolor* and *M. microannulata*, though Dick has suggested that two species of *Aedes* may be involved. The neurotropic virus may be of value in immunizing sheep and cattle, since on subcutaneous injection it causes almost no reaction.

CHAPTER XIX

PSITTACOSIS AND ORNITHOSIS

Definition.—Psittacosis is a disease of parrots, parrakeets and budgerigars transmissible to man. Ornithosis viruses are now known to infect a considerable number of birds, including finches, pigeons, gulls, fulmar petrels, willets (North American snipe) and ducks in Long Island and California. When the virus occurs in parrots and their relatives it is known as "psittacosis": in other birds as "ornithosis."

Epidemiology.—Outbreaks of psittacosis were at one time thought to have all arisen in Brazil, but no human cases have ever been reported in that country. There is no evidence that epizootics of this disease occur under natural conditions amongst the parrots in the forests of Brazil, but when these Amazon parrots, especially *Amazona aestiva*, are in captivity, and are transported under grossly insanitary conditions to Europe, the disease arises and is able to spread.

The disease sometimes causes the death of wild parrots in hundreds in Australia and in the Argentine. It very often operates in conjunction with food shortage. Sometimes only a few die each year.

The source of infection is usually the Amazon, though grey African parrots have been the apparent cause in some of the British cases. In Australia a number of parrots caught in New South Wales have been found infected, while in the Northern Territory the Gouldian finch (*Poliphila gouldiae*) and the long-tail finch (*P. acuticauda*) carry the virus. The Bengalese finch, a hybrid between *Aidemosyne malabarica* and *Uroloncha striata*, imported from China, is also a carrier, as are the siskin and crossbill. Among the *Ploceidae* the Java sparrow may show infection.

Possibly canaries, blackbirds and thrushes may occasionally act as carriers, and a disease resembling psittacosis has occurred in the Faroe Islands, where apparently it is propagated by the fulmar petrel, *Fulmarus glacialis* (Haagen and Mauer). During the last few years an atypical pneumonia had been described from these islands. It was confined to the middle-aged and occurred in summer and early autumn. Infection appeared to be contracted by the women who pluck and salt down the fulmar fledglings. (Rasmussen, 1938.)

The virus has been found to cause disease in pigeons in South Africa and in the United States, where at least five human cases have been reported in those who have had contact with sick birds.

Parrots may remain in a subacute infectious condition for several years. Direct infection from man to man has been noted, and in one English outbreak the doctor in attendance contracted the disease from his patient. House epidemics, too, are apparently not uncommon, particularly in Vienna, and, according to Gerlach, human beings may act as virus carriers after imperceptible infections. Human carriers are known and one man has remained infected for eight years.

An infective pulmonary condition with a general typhoidal picture occurring in definite groups should suggest psittacosis.

Ætiology.—The virus nature of psittacosis was worked out by Bedson and Western on the budgerigar (*Melopsittacus undulatus*), in which the disease is highly contagious. The virus can be transmitted by citrated blood or emulsions of liver or spleen. The blood contains the virus in the early stages of the disease

and as long as the tenth day. Besides parrots and parakeets, hens are susceptible. Mice are susceptible to experimental infection by intraperitoneal inoculation and, on intracerebral injection, develop encephalitis. These animals become acutely ill three or four days after injection and die of septicæmia with enlargement of the spleen.

The virus of psittacosis will pass Chamberland's L_1 , L_2 and Seitz EK filters. The size is 220–330 $m\mu$. Rabbits and guinea-pigs are susceptible to intracerebral inoculation (Rivers and Berry), as is also the Tasmanian devil (*Sarcophilus harrisii*). The virulence of the virus is increased by passage through mice, and an intracerebral inoculation reveals a definite neurotropic tendency (Gordon). The virus of psittacosis inoculated intratracheally or intranasally in monkeys produces a pneumonia similar to that observed in man (Rivers and Berry).

In parrots which have succumbed to a fatal dose of the virus, minute bodies are seen in the endothelial leucocytes in and near focal lesions. These Gram-negative bacillary bodies have also been found in human tissues and have been described by Levinthal, Coles, and Lillie as *Rickettsia psittaci*, and by some *Microbacterium multiforme*. The forms described in the early stages of infections of the mouse with psittacosis are developmental stages of the virus, which, according to Bedson and Bland, has a complicated life-cycle reminiscent of certain of the protozoa. These virus bodies, readily demonstrated by Giemsa's and Castañeda's stains, show considerable morphological variations. Some forms resemble bacteria: others rickettsiæ and, indeed, some authorities (Lillie) think the virus belongs to this group. Psittacosis virus, however, is best classified with the virus of lymphogranuloma venereum in a group termed by Rake the Chlamydozoaceæ.

Pathology.—Autopsy findings in man are those of a general septicæmia with inflammatory condition of the lungs. The spleen is normally enlarged and soft, with semi-diffuent pulp. The most striking changes are found in the lungs, which exhibit a peculiar hemorrhagic vesicular pneumonia, complicated by pulmonary thrombosis and a mucopurulent bronchitis in which bacteria are numerous. In the microscopic pathology one of the most striking features of psittacosis-pneumonia is the variation in type of the alveolar contents, often within the same microscopic field.

Symptoms.—Psittacosis in man is a severe illness with a high mortality (about 20 per cent.). All ages and both sexes are affected. It is, however, as a rule, comparatively mild in young people, increasing in severity with age. In those over fifty it is usually fatal. The duration of the disease is two to three weeks. Convalescence is protracted and tedious, and may be interrupted by temporary relapses or by femoral-vein thrombosis.

During the first week the patient may feel comparatively well, in spite of high pyrexia. The fever gradually rises in a step-like fashion to attain a maximum about the end of the first week. When recovery occurs the temperature falls by lysis. The early symptoms are epistaxis and generalized pains. Towards the end of the week the whole aspect becomes more severe; the patient suffers from profound exhaustion and tends to become somnolent and intermittently irritable; there is usually a troublesome paroxysmal cough, which persists to the second week. Scattered signs of consolidation, which may eventually involve the greater part of the lung, become apparent. Constipation now becomes manifest and gives rise to tenesmus and abdominal discomfort. The nervous symptoms consist of headache, drowsiness, apathy and mental depression. During the second week a state of semi-coma with muttering delirium sets in, to such an extent that life is despaired of, but when things appear at their worst, the temperature begins to fall by lysis, and in a few days the patient gradually shows signs of improvement.

Although the illness is usually severe, yet mild and even ambulatory cases have been recorded. The incubation period appears to be about eight to ten days, but may extend to sixteen days. In man-to-man infections it is generally about four days. Pyrexia is usually of the typhoid type, and occurs in all cases; some have a gradual rise of temperature of the "step-ladder" variety.

Epistaxis is early, usually on the first, sometimes as late as the eleventh to fourteenth day. Headache is a constant feature. Chills and rigors usually occur, and with the latter a temperature of 104° F. has been noted. Generalized influenza-like pains are the rule. The throat is usually sore and congested, and in a few cases the tongue is swollen and sore, in the condition known as "peribuccal œdema." The lungs are involved in almost every case, with a cough of varying intensity, but the sputum is scanty; it may be rusty, characteristic of lobar pneumonia. The physical signs in the lungs vary considerably. A relative bradycardia is the characteristic feature of the cardiovascular system. With a temperature of 103° F. the pulse is about 90 and this feature increases the typhoidal-like character of the disease and, indeed, the typhoid state accompanies all severe cases. Photophobia is also a feature, and, towards the end of the first week, most patients become lethargic, with stuporose appearance, sluggish speech, and blunted mentality.

"Rose spots," or similar skin lesions, have been noted in nine British cases, at varying periods from about the seventh to the thirteenth days. The spots were on the chest and abdomen, more rarely on the back, measured 2-4 mm. in diameter, and faded on pressure. Parotitis has been noted twice. The blood picture in characteristic psittacosis is not markedly altered. Ambulatory cases may have a fatal relapse.

Diagnosis.—On clinical grounds the diagnosis of psittacosis is not easy, as it has many features in common with typhoid. The gastro-intestinal symptoms may resemble those of that disease, but perforation and hæmorrhage never occur. The spleen is usually palpable in typhoid, but in only two out of 80 cases of psittacosis has this been recorded. With influenza, too, it has many features in common. Blood-cultures and agglutination reactions are completely negative in psittacosis, and inoculations of blood or sputum in the early stages of the illness will prove fatal to mice. Apart from isolation of the virus, the most satisfactory method of diagnosis is by the complement-fixation reaction. According to Bedson, the most satisfactory antigen is obtained from the spleens of infected mice, as it is essential to employ material that is rich in it. Antigen may also be prepared from cultures of the virus on agar-serum or chick-embryo medium. The technique is similar to that of the Wassermann reaction. It is diagnostic 8-12 days from the beginning of the disease, when it occurs 1 in 2-1 in 8 and in higher dilutions. There is a non-specific fixation with syphilitic sera up to 1 in 8.

CHAPTER XX

RABIES

Synonyms. Hydrophobia; Rage (French); Tollwut (German); Lyssa; Rabbia (Italian).

Definition.—Rabies is a disorder of dogs and other animals. Under natural conditions it is transmitted both to animals and man by inoculation of virulent saliva in the act of biting. The first explicit reference to rabies was set down by Aristotle about 385 B.C. in his *Historia Animalium*. The word rabies derives from "rabere", the Latin for "to rage."

Geographical distribution.—There is no part of the earth, where man and other terrestrial animals can live, where rabies cannot potentially exist. It occurs quite commonly in Greenland, Iceland and other Arctic countries, but it is possible that in the Far North a special modified form exists. In the tropics and subtropics, especially where jackals, wolves, foxes and wild dogs abound, a specially virulent form is sometimes prevalent. In South America and in the West Indies, cattle are commonly affected¹, constituting a reservoir of the virus, and in Jamaica the vampire bat plays an important part in dissemination. Australia is said to be free from this disease, and this freedom is ascribed to the peculiar fauna and the rigid quarantine which has been imposed upon dogs.

Rabies has been stamped out from Great Britain for over fifty years, except for small outbreaks among dogs when an animal has been smuggled into the country by aeroplane.

Animals susceptible to rabies.—All warm-blooded animals are susceptible, under favourable conditions, to experimental inoculation of the rabies virus; it is more commonly met in nature in those mammals which are subjected most often to the bites of dogs, wolves and foxes. Some species are rarely infected, either because they are seldom subjected to bites, or because they are provided with thick fur.

There is some reason to believe that skunks, weasels, stoats, civet-cats, and possibly the meerkat (*Cynictis penicillata*) may propagate the disease widely among their own kind, as does the dog. In South Africa also the yellow mongoose (*Galerella ochracea*) is a vector of rabies. These creatures are hunted by Kaffir boys who usually only succeed in capturing the sick ones, are often then bitten by them, thus transmitting the virus. The susceptibility of rats to subcutaneous inoculation led to the opinion that these animals might also be capable of perpetuating this disease in nature, but of this there is little evidence. Therefore, in South Africa meerkats act as a reservoir, while in the United States grey squirrels may play a similar rôle.

In Canada there have been large epidemics amongst foxes, wolves and other wild animals during the last three years (1956). Birds are relatively insusceptible to inoculation and this is said to be due to their high body temperature. Frogs are said to be susceptible.

The alleged disproportionate prevalence of rabies during certain seasons of the year appears to have little foundation in fact. In India one-third of the cases are inflicted by jackals, 50 per cent. of mad dogs excrete the virus in the saliva, whilst rabies following scratches is rare.

¹ In South America rabies in cattle is—perhaps wrongly—termed "Mal de Caderas."

Ætiology.—The most generally accepted view of the infection is that the virus of rabies, upon its introduction beneath the epidermis, finds its most favourable medium for propagation in nerve-endings and fibres torn in the region of the bite. Along the course of the axis cylinders it develops and travels, without disturbing their function, until the central nervous system is reached. The virus is strictly neurotropic (*septinëvrite*), although Marinesco and Stroesco consider that the main path of dissemination is by the lymphatics. Finally, the cells of the central nervous system are attacked, the first effect being excessive stimulation, followed by destruction. At the same time a neurotoxin is produced which is responsible for some of the symptoms. Nerves leading from the site of the inoculation to the central nervous system have been shown to become progressively infectious in ascending segments, while complete section previous to inoculation confines the toxin to the lower segment. The blood and lymph appear to be incapable of taking up the toxin from the site of inoculation.

Street virus ("*virus des rues*," "*Strassenvirus*") is the strain found in the virulent nervous tissue infected by the natural disease; its virulence is very variable and, when inoculated subdurally into rabbits, it causes symptoms of rabies after a variable period of more than fourteen days. Inoculations should, if possible, be carried on for several passages, till the nature of the virus becomes clear. Considerable variation in street virus occurs, some strains showing rapid adaptation to the central nervous system. Certain strains from wolves are known as *renforcé* and produce paralysis in rabbits after a short incubation period.

Fixed virus (*virus fixe*) is modified from the street virus by passing through a long series of rabbits. In this manner its virulence becomes greater for these animals, so that finally they develop the disease after a constant or "fixed" period of inoculation, after which no further *passages* can reduce the incubation period below this span. This virus does not normally produce Negri bodies. The mouse, however, appears to be the most suitable animal for rapid diagnosis.

Negri "bodies."—Negri originally described certain oxyphilic granules in the nerve-ganglia cells of the *hippocampus major*. Although they are probably of the same nature as the cytoplasmic inclusion bodies found in association with other ultramicroscopic viruses, yet Negri bodies are admittedly very constant in rabies, peculiar to it, and useful for diagnosis.

Moulton has elaborated a technique by homogenization-centrifugation in sucrose. Negri bodies give positive reactions for protein, arginine, tyrosin and *alpha* amino-acids. This technique has proved successful in isolating many Negri bodies from host cells which with isolated nuclei form a grey button at the bottom of the centrifuge tube.

Rapid diagnosis with phase contrast microscope method can be performed in 15 minutes by examination of frozen sections of Ammon's horn, measuring 20–50 μ after fixation in Dubosq-Brasil-Bouin reagent at 60° C. or for 5 minutes in 10 per cent. boiling formol saline. The Negri bodies are greyish-green, sharply defined showing their internal structure and are thus visible in the cytoplasm of certain nerve cells (Cajal and Mateescu 1955). A complement-fixation test, as devised by Ando and colleagues, provides an additional aid to diagnosis. The antigen is prepared from fresh or glycerinated brain substance. The anti-rabies' serum is produced by hyperimmunizing rabbits with inactivated, then with live virus. When the reaction is negative the case is not rabies, but if it is so the reaction is positive (Depoux and Merveille, 1956).

Covell and Danks, after micro-incineration and other studies, concluded that the Negri bodies arise from constituents in the nerve-cell as a result of the virus. They are not present in every case of rabies, but when a person has been bitten by an animal having symptoms suspicious of rabies, preventive treatment

should at once be instituted. Inoculation tests have shown that this practice is sound. The custom of killing suspected animals immediately after they have bitten their victim is not recommended, as this practice operates against the demonstration of Negri bodies which may be present in the later stages of the disease. Furthermore they have to be distinguished from the Lentz bodies¹.

Location of the virus in the body.—The central nervous system and the peripheral nerves contain the virus with constancy, but infectiousness is variable in different parts of the nervous system. It was found by Nitsch that 0.1 mgm. of the brain cortex (*fixed virus*) was lethal to rabbits in seven to nine days, whilst 0.5 mg. from the centre of the cord was not virulent, though 1.0 mgm. was. The medulla, for instance, is five times more virulent than the rest of the cord. The salivary glands of dogs are constantly infectious. The generally accepted view is that the virus finds its way to these glands by way of the nerves and, according to Remlinger, the saliva of a dog may remain virulent five days after apparent recovery from rabies. In man the salivary glands are seldom invaded. The blood is non-infectious, either in man or in experimental animals. There is no evidence that the virus can be conveyed to the foetus. Neither the milk, urine, liver and spleen, nor spermatic fluids ever harbour it.

Cultivation of the virus.—The Swiss mouse and white mouse are the animals of choice for experimental work; the former is ten times more susceptible for rabies virus than the rabbit or guinea-pig and is incomparable for assessment for the immunizing power of different antirabies vaccines.

Desiccation does not attenuate, but preserves the rabies virus. Now, in almost every country, the classical method of Pasteur and dilution method of Höegyes have been replaced by the use of etherized or phenolized vaccines which retain their immunizing properties for months and can be despatched far and wide. Paralytic accidents complicating antirabic treatment are on the increase. It is important to distinguish between "rage de laboratoire," where the virus used in treatment is recovered at autopsy, and the "paralytic accidents," which, whilst usually less serious, are much more frequent. In most countries cattle, horses, sheep, pigs and goats are being successfully immunized after having been bitten by rabid animals.

Powell and Culbertson have succeeded in cultivating fixed rabies virus in embryonated duck's eggs. The eggs were infected intra-amniotically and growths harvested after 14 days. Apart from the embryo itself a degree of infectivity could also be detected in the extra-embryonic fluids. The strains have been carried on for three generations and seem to have lost some of their virulence for mice, and when used as a vaccine this material protected against 700 L.D. as determined by the mouse potency test.

Bat Rabies (The Trinidad disease) (Paralyssa).—Hurst and Pawan (1930) described a curious paralytic form of rabies in Trinidad and it has been found in Mexico, and also in British Guiana on the Mazaruni river. It appears to affect, and be spread by, the vampire bat, which in South America and in the Antilles feeds indiscriminately on the blood of man and cattle and has been reported in S. California. Oviedo in the 16th century described the death of 40 Spaniards from the bites of vampire bats. The disease was first noticed in cows: subsequently five cases were discovered in man, and the virus was transmitted to monkeys. This disease is apparently identical with "mal de caderas" of South American cattle, but is probably better termed South American *lyssa*. Some doubt has been expressed whether the bat at first identified by Pawan was the vampire or a harmless species of the genus *Artibeus*, but Lima (1934) in Brazil by direct experiment, brought forward evidence that, in the State of Santa

¹ Lentz bodies occur in the sympathetic ganglia and extracellularly between ganglion cells of rabbits injected with fixed virus.

Catherina, epizootics of paralyssa are prevalent in the favourite haunts of vampire bats (Desmodidae) and that the transmitter is the local species (*Desmodus rotundus*). The virus may be demonstrated in their saliva and they act as carriers for considerable periods. Kraus and Duren suggested the designation "*Paralyssa*" for this form.

In recent years more apparently innocuous bats have been incriminated. In 1953 rabies virus was isolated from the brain of the yellow bat (*Dasypterus floridanus*) killed in Florida whilst attacking a boy. Subsequently it was obtained from five other bats which were apparently normal, including one Seminole (*Lasiurus seminola*), in an insectivorous species, *Tadarida mexicana*, and *Chilonycteris personata* in Vera Cruz. Since that time three gnat-eating genera have been proved infected in nature, such as *Phyllostoma*, *Artibeus* and *Hemiderma* (*Carollia*). These attacks by rabid bats all occurred in Texas, the first, early in April, 1953, in San Antonio, the second and third in May and July, near Austin. One of the victims was a Health Department Officer—a field epidemiologist—who had been collecting cave-dwelling bats in Central Texas to be examined for rabies. Further investigation revealed the disease at Carlsbad Caverns and that, during the last 1½ years, out of 10,000 bats in 15 states 150 were positive for rabies and all were insectivorous. This probably represents a recent northward invasion from the vampire-bat rabies areas in Latin America. It is known that Mexican free-tailed bats of the south western states migrate deep into the vampire countries and probably share the same winter caves. The problem is complicated by the fact that some vampires are capable of transmitting the disease for long periods without showing any signs of illness.

Incubation period of rabies.—This is remarkable for its length and great variability. In nature it is seldom under ten days, but may extend to a year, or even to three, though in the majority of cases the disease develops before the end of the third month.

The length of the incubation period is influenced by the following factors.

- (i) The species of animal: it is usually longer in man than in the lower animals.
- (ii) The site of the inoculation: the shorter the distance from the brain, the shorter will be the period of latency, whilst females exhibit a shorter period than males, and children than adults.
- (iii) The severity of the wound and the physical condition of the patient have an undoubted influence.

Webster gives the incubation periods as:—

Bites on head, face and neck	30 days.
„ upper extremity ..	40 „
„ lower extremity ..	60 „

Symptoms and clinical course.—Rabies presents two distinct clinical types: the furious or excited, and the quiet, "dumb" or paralytic. Some distinguish four types of the disease: cerebral, medullary, cerebellar and sympathetic.

The excited or furious type.—The onset of rabies is usually rapid; the patient shows some psychical change very early, becoming anxious, melancholy, and possessed of strange presentiments. Sleep becomes impossible. Soon, local numbness, twitching, and a sense of itching progress from the wound, which becomes engorged and tender. Sometimes the first symptom is a strange sensation in the throat or a sense of constriction of the fauces.

The mental symptoms may be purely hysterical, and many cases have been recorded in which the onset is determined by mental shock, though fright and terror may be regarded as manifestations of the disease. An initial rise of temperature is perhaps the most constant early sign.

Symptoms may last several days before the outbreak, but usually only twenty-four to forty-eight hours. *Hydrophobia*, the outstanding symptom, prevails in

the great majority, and arises from extremely painful spasms of the organs of deglutition and respiration induced by attempts to eat and, especially, to drink. These spasms are so agonizing that they exceed, possibly, all other forms of human suffering; the sight or smell, or even the sound of liquids, is sufficient to excite an attack. When an effort is made to gulp down a small quantity of liquid it is expelled, with an anguishing spasm of the throat and larynx. This condition is a state of hyper-susceptibility of the nerve-cells to external stimuli. Draughts of air may bring on a convulsive seizure; skin and tendon reflexes are exaggerated; respiratory spasms involve the thoracic muscles and cannot be relieved by intubation. Solid foods are usually more readily taken than fluids.

The disease progresses rapidly. In the majority of instances there may be periods of latency which cause hope of recovery and doubts of the diagnosis. The mind is usually exceptionally clear, questions being answered with intelligence until the voice becomes indistinct and words unintelligible. But there are periods of excitement which may be truly maniacal; the patient may injure or destroy any objects near at hand, but there is seldom any tendency to injure other persons. Sexual excitement, accompanied by priapism, is frequent. The voice usually becomes hoarse; the strange sounds emitted during expectoration at the onset of the seizure have given rise to the popular conception of "barking like a dog."

The convulsive seizures become more and more pronounced until paralysis leads to death. The muscles, which have been racked to the limit of endurance, become limp, and the face, previously expressive of terror and suffering, becomes expressionless. There is usually an excessive secretion of rosy saliva, which the patient is unable to expel.

The paralytic type in man.—Because symptoms are less marked than in the violent type, this undoubtedly remains unrecognized in many cases. For a time the mere existence of this form was forgotten. Pathologically it has been attributed to infection with a large amount of virus and to the involvement of the spinal cord rather than the brain. The onset takes place with high fever, general malaise, headache, and vomiting; afterwards there is localized pain, especially in the bitten parts; a heaviness and numbness of these regions follow, then ataxia, weakness, and finally paralysis. Girdle sensation is usually present.

The paralytic form is very common in herbivora, but horses present the most agonizing type of the furious form.

Mortality in untreated and treated persons.—Once rabic symptoms develop the disease is invariably fatal and the average mortality varies from 5-15 per cent. It is highest from wolf-bites, more especially on head and face and higher in deep than in superficial wounds. Remlinger considers that of 1,000 persons treated in an antirabic institute for dog-bite probably only 500 have been bitten by rabid dogs as the death rate in such persons would be about 15 per cent. We may expect 75 out of the 1,000 would die of rabies, if untreated. The mortality in treated persons is about 5 per 1,000 and it appears that antirabic treatment saves 70 per thousand so treated. The mortality from untreated wolf-bite is 60 per cent., and it is rare for these animals to bite unless they are rabid; yet the mortality in cases of wolf-bite which have been subjected to treatment is not more than 15 per cent. (Remlinger). It is therefore justifiable to continue to regard antirabic treatment as of some value in the prevention of rabies, though it may not act by the orthodox method of active immunization.

Immunity.—Natural immunity to rabies is exhibited by a number of lower vertebrates; occasionally in mammals an *individual immunity* may be observed, and a state of *hereditary immunity* has been, somewhat doubtfully, described by Remlinger and Konradi.

Much more is known about acquired immunity. Man and animals may be rendered immune by inoculation with modified virus of rabies; secondly, their blood acquires "rabicidal" properties, that is, the power to render inert the virulent material exposed to its action *in vitro*.

Immunity to rabies can be conferred by increasing doses of filtered emulsions, especially those exposed to high temperatures.

Levaditi and Stoel showed that the virus of rabies is maintained, and probably multiplies, when placed *in vitro* in contact with cellular elements. The virus develops in contact with embryonic cerebral tissue *in vitro*.

The virus is more virulent in rabbits, inasmuch as it causes the disease more rapidly, but at the same time it loses virulence for animals higher in the taxonomical scale. It is assumed that, by passage through rabbits, the virus becomes augmented, hence the early onset and the paralytic symptoms. Its resistance to the inimical action of the body juices is thought to be reduced; hence the harmlessness of subcutaneous injection. The argument in favour of the toxin of rabies being an ultramicroscopic virus is the production of symptoms of fever, emaciation, and cachexia after passage through a filter. Glusman, Solonjowa and Predtetschenkaya have found that the virus can pass through Chamberland bougies L_2 and L_3 . Occasionally during inoculations, or soon after, paralytic symptoms appear, apparently not directly due to rabic infection. Paralysis of the Landry type is often noted. These paralytic accidents, which are associated with demyelination in the nerve sheaths, are probably of an allergic nature.

There are other peculiarities of the rabies virus toxin; thus, the spinal cord of the rabbit, when dried until it has lost its infectiousness, has also entirely lost its immunizing properties.

Diagnosis and differential diagnosis.—Very often it happens that no history of infection may be obtained until late in the disease, or until after death. There are instances where the victim has died of rabies, yet the infecting dog has recovered. In assessing the length of the period of incubation, well-authenticated cases of rabies may commence as early as ten days after exposure, but hysterical manifestations come on a few hours or days after assumed exposure. The mental behaviour of the patient during the probationary period may assist in diagnosis, but many cases show no disturbance whatever until tell-tale signs develop. The chief difficulty is, of course, with hysterical manifestations, and it is stated that hypersensitiveness to draughts of air, common in true rabies, is not evoked in hysteria, so that fanning a patient may produce a convulsive seizure. Tetanus and mania may also simulate rabies. The absence of trismus in one, and of convulsive seizure in the other, will help. Some paralytic cases of rabies may resemble Landry's paralysis.

In the lower animals there is a variety of diseases, such as dog distemper, dog hysteria, or brain tumour, which may simulate rabies. The hysteria of dog distemper and true dog hysteria have to be differentiated. Then there is the *pseudo-rabies* or "mad itch" of Aujeszky. This virus is much more resistant to desiccation. Remlinger and Bailly found that the intraocular route is the most practical method of differentiation in experimental infections, because in *pseudo-rabies* the issue develops suddenly, which is not the case in true rabies. The infection is transmitted along the axis cylinders of the nerves, reaching the ganglia and segments of the cord, producing this degeneration which is probably responsible for the itching from which the disease takes its name. *Pseudo-rabies* has occasionally occurred in men, as a result of handling infected animals. It is a non-fatal disease and is characterized by intense itching.

Cases of "psychological" rabies have occurred in medical men and veterinarians bitten by dogs suspected of having rabies. Apart from psychological symptoms, there are no nervous changes.

TREATMENT

Indications for treatment are :—If the biting animal is clinically rabid, especially when confirmed by laboratory tests, in endemic areas after the bite of a stray animal or dog, or after handling an animal diagnosed as rabid, when there are fresh abrasions of the skin contaminated by saliva.

(a) **Treatment of the developed disease.**—As in other virus diseases, a potent antirabic serum has no effect once the symptoms have begun. Therefore, fully developed rabies in man must be treated on symptomatic grounds. Chloroform inhalations are given for control of painful spasms; chloral and bromides *per rectum* and, if possible, curare, subcutaneously. Morphia is apt to increase the mental excitement and suffering. Where the patient cannot swallow food, rectal alimentation is to be preferred to feeding by stomach-tube. Intubation or tracheotomy are probably both useless for the relief of dyspnoea and suffocation. Mechanical restraint is generally unnecessary and should not be resorted to except in violent maniacal forms. The attendants must preserve a calm and pleasant demeanour and, when speaking of the disease, should do all possible to reassure the patient. Penicillin and the sulphonamides are useless.

(b) **Treatment by hyperimmune serum.**—There is some reason to believe that hyperimmune serum, when given in the early stages may have a beneficial effect. Baltazard and Bahmanyar (1954) from Teheran have given an account of 29 human victims bitten by a rabid wolf. The mortality was 60 per cent. in untreated cases. The 18 with head injuries received hyperimmune serum, in addition to vaccine. In those treated with daily vaccine no antibody appeared till the 19th day. On the other hand in the patients who were given serum it was present early. The vaccine was made from the egg-adapted Flury strain. It is claimed that this experience has put this combined treatment on a sound footing.

(c) **Prophylactic treatment of person exposed to infection.**—Cauterization of the infected wound has been practised since time immemorial and, when properly carried out, it is undoubtedly of some benefit. It has been shown by experiment that the incubation period is prolonged, even when it does not prevent extension of the infection, and thus permits more time for establishment of immunity by antirabic inoculations. Fuming nitric acid is useless. The best local treatment is the application of 1 per cent. benzarkonium chloride ("zephyran"). Experimental work on guinea-pigs shows that application of iodine, or washing with soap and water is as effective as cauterization.

(d) **Preventive inoculation.**—The Pasteur treatment for the prevention of rabies in exposed persons is designed to confer immunity during the period of incubation. The production of this immunity is necessarily a long process, but, fortunately for humanity, the incubation period of rabies is normally much longer. In persons in whom, from a combination of factors, the incubation period is very short, the Pasteur treatment fails.

The principle upon which the Pasteur treatment is based may possibly rest upon the production of immunity by inoculation of modified rabies virus. However, it is much more probable that the value of antirabies inoculation depends on the interference phenomenon where the killed or attenuated virus particles prevent the virulent particles from reaching susceptible nerve cells. This has been finally accomplished by serial passage of the virus through rabbits until a fixed degree of virulence has been reached, and secondly, by its attenuation by desiccation. The first of these processes is the more important and the one most frequently employed at the present time. The following methods have been employed:

Laboratories producing antirabic vaccine must periodically test the properties of the strain, by neutralization tests with antiserum samples in mice. Mice must be immunized with vaccine ready for use by intracerebral injection. In such tests it is customary to inject the subsequent or "challenge" dose of live virus by a route which kills all control animals.

The mouse immunity test vaccine to be assayed is diluted 1 : 10. Thirty-two week-old mice are required. Canine vaccine is given intraperitoneally to each of sixteen. For vaccines for human use mice are given 3-6 injections. Three weeks after the first injection of vaccine sixteen control mice are divided into four lots and injected intracerebrally with 1 : 10, 1 : 100, and 1 : 1,000 (40-50) doses. Both test and the sixteen control mice are examined for 60 days. Vaccine effective for mice is equally effective for dogs. Phenolized vaccines, however, fail to immunize mice against a subsequent intracerebral challenge. It is difficult to protect laboratory animals by antirabic treatment after injection.

(1) *The dilution of fresh-fixed virus*, a method introduced by Hőgyes, who maintained that attenuation could be more accurately controlled by diluting the fresh virus with salt solution and increasing the dosage, as treatment progressed, by increasing the strength of the emulsion. An improvement suggested by Harvey and McKendrick is to take smaller amounts of an original emulsion of fixed virus prepared from the spinal cord of a rabbit dead of a fixed-virus infection, rubbing it up with sterile salt solution in the proportions of 1 in 100. Dilutions are prepared varying from 1 in 200 to 1 in 10,000. The dilutions are then used for immunizing. For severe cases, such as head or face wounds, as many as five injections are given daily in dilutions varying from 1 in 2,000 to 1 in 10,000, in the first four days, and subsequently, to the twentieth day, two or three times daily. Formulæ have to be devised to suit individual cases.

(2) *Fixed virus attenuated by drying*.—The original method of Pasteur, and one still most extensively practised, has the advantage that it may be administered by private practitioners at some distance from the laboratory, since dried virus can be preserved by glycerinization, and despatched in this condition. The original scheme of Pasteur has been greatly modified, according to the time consumed by the treatment, by dispensing with some of the more attenuated cords, and by increasing or diminishing the dosage at individual injections. In the first four days two 3 ml. injections are made daily of emulsions of cord dried *in vacuo* 14, 13, 12, 11, 10, 9, 8, 7 days respectively. The total course of treatment is twenty-one days.

(3) *Fixed virus acted on by glycerin*.—While glycerin possesses the power of conserving rabies virus in an active state for a month or more, on prolonged exposure this virulence is lost, although the immunizing power may be retained. This is the method which was advocated by Calmette, although rarely is this immunity sufficiently substantial to withstand subdermal inoculation tests with the fixed virus.

(4) *The carbolized fixed virus* is used at Kasauli and other stations in India. The whole brain is removed and a solution containing 1 per cent. of phenol in 0.85 per cent. salt solution is mixed and placed in a mortar in an incubator at 37° C. for twenty-four hours—sufficient to kill the virus. The suspension is stored at 0° C. while tests are being carried out, and is used as a vaccine after two to three weeks' storage.

Before inoculation the suspension is again diluted with an equal part of 0.85 per cent. salt solution, so that it finally contains 0.5 per cent. brain substance. Each patient, however severely bitten, receives 4 ml. of this suspension daily for a period of fourteen days.

In India those at risk receive 2 ml. daily for seven days; those most at risk 10 ml. for 14 days. The antirabic treatment fails in severe wounds of head and

face. McKendrick gave the overall mortality in treated persons as 0.33 per cent., in Europeans as 0.15 per cent., and in non-Europeans as 0.56 per cent.

(5) *Inactivated antirabies vaccine*.—Yaoi (1954) and colleagues in Japan have prepared *Merzonin* (M) vaccine. To determine the concentration of M suitable for the preparation of this potent vaccine, emulsions of guinea-pig brain infected with rabies virus were treated as follows: 20 per cent. emulsions with 0.1 per cent. M; 10 per cent. with other dilutions. All were placed in the incubator at 37° C. for 5 days to ensure complete inactivation. The effect of storage on the antigenic potency of the vaccine was minimal, as it (10 per cent. brain emulsion + 0.1 per cent. M) kept its potency for at least one year in the refrigerator (4° C.), in contradistinction to other vaccines. *Merzonin* vaccine is prepared by suspending in normal saline (pH 7.2 to 7.6) 10 per cent. of finely ground guinea-pig brain infected with Nishigahara strain of rabies fixed virus, and, after adding the organic mercury compound, *Merzonin*, in 0.1 per cent. concentration and exposing the whole to a temperature of 37° C. for 5 days. The vaccine is administered intradermally in a dosage of 0.2 ml. on each of 10 consecutive days. Apart from local reactions there have been no ill-effects.

The indications for the Pasteur treatment.—All persons who have been bitten by rabid animals, or who have had open wounds or scratches contaminated with the saliva of rabid animals, should receive the treatment. If, however, the suspected animal remains alive and well for ten days after the bite, treatment may safely be discontinued. In persons who have drunk the milk of infected cows, the possibility of infection is very remote, as gastric juice destroys the virus. Everyone who has been bitten by animals presenting symptoms of rabies should receive antirabic treatment, whether or not the suspicion is confirmed by histological examination, and pending the result of inoculation tests. Those persons who are bitten by animals, which do not show any of the symptoms of rabies, should not be exempt from the necessity for treatment until the biting animal, which should be carefully confined and watched, is shown to be free from the disease. It must be emphasized that histological examination is conclusive only when Negri bodies are demonstrable in the central nervous system.

The results of the Pasteur treatment.—Even with the most careful assessment of the results of treatment, it is extremely difficult to determine exactly the mortality-rate after the bite of a rabid dog. In untreated persons the estimated mortality is about 14.8 per cent. in 122 persons (Doebert, 1909). In 1935, 118,000 people received prophylactic inoculation. Figures published by the League of Nations show that from 1929–1935 only 0.4 per cent. of 524,258 people receiving antirabic treatment died from rabies. Though many were not bitten by rabid animals, nevertheless the impression remained that mortality would have been greater if they had not been so treated. As a general statement, it may be said that the total mortality of bitten persons subjected to antirabic inoculations is about 1 per cent., of whom half could not, on account of the short time permitted for the establishment of immunity, have been expected to live. Comparison of statistics from various Institutes giving antirabic immunization does not show any marked preponderance in favour of any particular method as there are so many variables to be taken into consideration, such as the situation of the bites, the interval between bite and the initiation of treatment, the thoroughness with which rabies was diagnosed in the biting animal and the length of time during which the patient was followed up after the end of treatment.

There is growing evidence that the Pasteur treatment is not a true immunization, but is the result of immunization.

Myelitis following antirabic vaccine is a rare complication. Transverse myelitis, which may be transient, has been recorded. Russell (1946) has described a case in which myelitis terminated in bulbar palsy. Thus McFadzean and Choe in

Hong Kong reported that in the years 1949-1952 14,119 patients were given phenolized simple vaccine and 17 neuromyolytic accidents occurred: an incidence of 1: 831. Two histopathological pictures were represented. Group I with perivascular myelinoclasia produced the clinical picture of myelitis, meningo-encephalitis or encephalitis. Group II with polyradiculo-neuronitis produced clinical pictures ranging from 7th nerve palsy to general involvement of all nerves and muscles.

The first group are an expression of sensitization reaction to the nerve substance in the vaccine, a conception strengthened by the response to ACTH and cortisone. The pathogenesis of the second group is unknown.

Immunization of animals.—In South America, cattle in many areas are being immunized prophylactically, while in certain towns dogs have been similarly treated. During the rabies outbreak in Singapore in 1937, arrangements were made to immunize the whole dog population, amounting to approximately 13,000. A killed virus should preferably be used for animal immunization.

Prophylaxis.—Experience has abundantly shown that in most instances complete eradication of rabies can be reached and freedom from the disease maintained by concentrating attention on the dog.

By quarantine measures, destruction of stray dogs, even with the aid of canine vaccination, systematically applied, the natural trend of the disease towards self elimination can be encouraged. In recent years the efficacy of both living and killed vaccine in canine prophylaxis has been amply vindicated. This is a valuable measure in countries faced with the problem of enzootic rabies. It is difficult to evaluate the rôle played by canine prophylaxis when consideration is paid to the observations made by Ramon.

Belgium, France, Great Britain, Ireland, Norway, the Netherlands, Sweden and Switzerland, have succeeded in eliminating rabies without the aid of canine vaccination. But in the United States, where canine vaccination has long been practised, rabies shows no signs of decreasing. It is generally agreed that canine vaccination is incapable *per se* of eradicating rabies as it can obviously have no effect on animals which constitute the wild life reservoir of the disease.

In the control of rabies too the fox is important in Central Europe and South America, the skunk in U.S.A., the mongoose in Porto Rico and the Union of South Africa, the wolf in Central Asia, and jackals in Africa and the Middle Eastern countries.

Examination of suspected material for evidence of rabies.—The material generally consists of the head of some animal, most frequently of the dog, and should be wrapped in cloths soaked in bichloride of mercury or other germicidal solutions, while for microscopic examination material may be sent already fixed in weak alcohol. For inoculation, the medulla which has been immersed in glycerin is suitable. Sections give better results than smears, but naturally take longer to prepare. If grossly contaminated with bacteria, the tissues should be treated with ether in a concentration of 10 per cent., which does not destroy the virus when allowed to act for two hours at 4° C.

In order to locate the hippocampus, or *Cornu Ammonis*, the brain is placed upwards, with the temporal lobe lifted outwards from the median line until the cornu comes into view as a long cylindrical whitish body tapering at its anterior end. Smears are made on slides or cover glasses by crushing a small section of brain matter between two of them and drawing out under gentle pressure to produce a fairly thin film. After fixation they are stained in Unna's polychrome methylene blue for three minutes and examined after differentiation in 95 per cent. alcohol. Negri bodies stained in this way take on a magenta

colour. In recent years it has been suggested that the mesencephalon, or oculomotor nucleus, is a more favourable site than the hippocampus. Morgan and McKinnon, however, found that in naturally infected dogs and monkeys, the hippocampus should be regarded as the site of election.

Another technical method is subdural inoculation, which is performed by a small trephine or jeweller's drill, to effect an opening into the skull large enough to admit a needle. The mouse is more suitable than the rabbit or the guinea-pig. Negri bodies can be demonstrated in mouse brains eight to nine days after inoculation (Sulkin and Nagle).

CHAPTER XXI

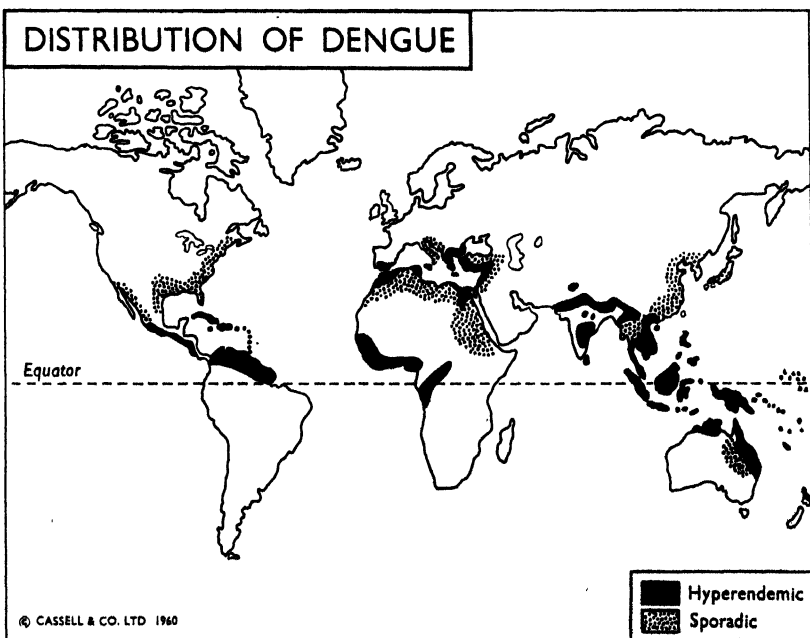
DENGUE

Synonyms. Dandy Fever ; Breakbone Fever ; Chapenonada (Philippines) ; Sellar Fever.

Definition.—A specific fever conveyed by *Aedes ægypti*, and some other ædine mosquitoes, occurring usually as a rapidly spreading epidemic. Throughout the febrile stages, and often subsequently, severe rheumatic-like pains are prominent. The disease in its active form lasts about a week, and is attended with little, if any, mortality. Severe cases may simulate yellow fever.

Geographical distribution.—*Europe.*—Greece (epidemic of 239,000 cases in September, 1928), Turkey. *Asia.*—Syria, India, Ceylon, Burma, Cochin China, S. China, Indonesia, Philippines. *Africa.*—Egypt, Libya, Tunis, Morocco, Tangier; whole of coastline as far south as Loanda on the West and Durban on the East; Tanganyika; Madagascar; Mauritius and other islands of the Indian Ocean. *Australia.*—N. Territories and N. Queensland (Brisbane), New Guinea, Fiji, Samoa and other Pacific Islands. *America.*—Central and S. America as far south as São Paulo in Brazil. N. America, Charleston and Philadelphia (epidemics in 1922–23 and again in 1984); W. Indian islands (Map VIII).

Epidemiology and endemology.—The characteristic of dengue fever is its tendency to recur at intervals of years, sometimes in pandemic waves,



MAP VIII

inflammation and general lymphadenitis were the special features. Serous effusions in the neighbourhood of joints and inflammation of the crucial ligament of the knee have been noted, while myocarditis, nephritic lesions with degeneration of the cells of the convoluted tubules, and a specific encephalitis with leucocytic blocking of some of the cerebral capillaries, have also been recorded.

Symptoms.—Attacks in Europeans are more severe than in the indigenous inhabitants. The *incubation period* of the naturally acquired fever seems to be somewhat variable, generally from five to nine days, though sometimes it appears to be shorter. The course of the disease may be divided into three periods: stage of invasion, lasting two to three days; stage of remission, lasting twelve hours to three days; terminal fever and eruption.

Stage of invasion.—An attack of dengue may be preceded for a few hours by a feeling of malaise or, perhaps, by painful rheumatic-like twinges in a limb, toe, finger or joint, which, when confined to the knee-joint, are excruciating. Usually it sets in quite suddenly. Sometimes the fever is ushered in by a feeling of chilliness or even by a smart rigor; sometimes a deep flushing of the face is the first sign. However introduced, the fever rapidly increases. The head and eyeballs ache excessively, and some particular limb or joint, or even the whole body, is racked with peculiar stiff, rheumatic-like pains, which, as the patient soon discovers, are much aggravated by movement. The loins are the seat of great discomfort, amounting in some cases to actual pain; the face—particularly the lower part of the forehead, round the eyes, and over the malar bones—may become suffused a deep purple; and often the skin over a part or the whole of the body, and all visible mucous surfaces, are more or less flushed. The mouth and throat are usually erythematous with small superficial erosions. The eyes are usually much injected. This congested, hyper-sensitive and erythematous state of the skin constitutes the so-called prodromal eruption. There may be a *tache cérébrale*.

The cerebro-spinal fluid is under pressure; there is some increase in the albumin and a considerable increase in sugar, but no increase in the chlorides and no marked cellular reaction. This hypertension is probably the cause of the severe headache, stiffness of neck, pain in the back and bradycardia which supervene in the stage of reaction.

These symptoms becoming in severe cases intensified, the patient, in a few hours, is completely prostrated. His pulse rises to 120 or more; his temperature to 103° F. (Chart 20), in some cases to 105°, even to 106° F. He is unable to move owing to intense headache, severe pain in limbs and loins, and profound sense of febrile prostration. From time to time the skin may be moistened by an abortive perspiration, but for the most part it is hot and dry. Gastric oppression is apt to be urgent, and vomiting may occur. Gradually the tongue acquires a moist, creamy fur, which, as the fever progresses, tends to become dry and yellow. In this condition the patient may continue for from one to three or four days, the fever declining somewhat after the first day.

In a proportion of cases, and particularly in certain epidemics, crisis

does not occur, the fever slowly declining during a period of three or four days. In some epidemics enlargement of the lymph nodes, particularly of the cervical group, has been noted, especially by Helsler (1937), and more recently by Findlay and Brookfield (1948) in the Gold Coast and Nigeria. In one epidemic in St. Thomas in the Virgin Islands adenitis was recorded in 62.5 per cent.

Stage of remission.—When the second stage is established and the thermometer has sunk to normal, the patient is sufficiently well to leave his bed and even to attend to business. The tongue clears, and the appetite and sense of well-being return to some extent.

Terminal fever and eruption.—The state of comparatively good health continues to the fourth,

fifth, sixth or even to the seventh day, counting from the onset. Then there is generally a return of fever, slight in most cases, more severe in others. With the recurrence of the fever a rubeolar eruption, consisting of dark, dusky spots, appears. The pains likewise return, perhaps in more than their original severity. Though the fever subsides in a few hours, the eruption, at times very evanescent, may be apparent for two or three days longer, to be followed very frequently by an imperfect furfuraceous desquamation.

Characters of the eruption.—The terminal rash of dengue possesses very definite characters. It is absent in a very few cases, but in many, being slight, it is overlooked. Usually it commences on the palms and backs of the hands, extending for a short distance up the forearms. It quickly extends, and is best seen on the back, chest, upper arms (Plate VII), and thighs. Here it appears at first as isolated, slightly elevated, circular, reddish-brown, rubeoloid spots, $\frac{1}{8}$ to $\frac{1}{2}$ in. in diameter, thickly scattered over the surface, each being isolated and surrounded by sound skin. There may be a general coalescence, isolating here and there patches of sound skin; in this case these give rise, at first sight, to the impression that they constitute the rash—a pale eruption, as it were, on a scarlet ground, giving an appearance “midway between scarlet fever and measles.” The spots disappear on pressure, and never, or rarely, become petechial. Usually the face escapes. They fade in the order in which they appear—first on the wrist and hands; then on the thighs and body; lastly, on the legs and feet, but they may still be visible three weeks after recovery from fever. Desquamation may persist for two or three weeks. In many it is trifling; for the most part it is furfuraceous.

At this stage the characteristic slowing of the pulse, which may fall as low as 44 per minute, and leucopenia, which may reach 1,200 leucocytes, are noted; the latter is mostly due to a marked decrease of the polymorphonuclear cells, which may be reduced to 40 per cent. (with

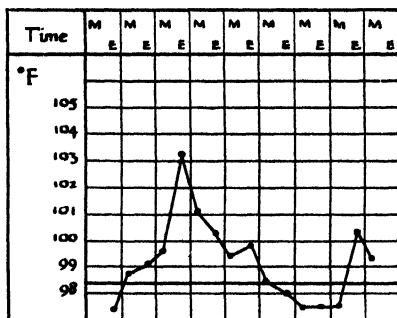


Chart 20.—Dengue. (After Cleland and Bradley.)

shift to the left), and to a relative increase of the lymphocytes (up to 58 per cent.).

Rheumatoid pains persist for some time after convalescence has been established. They are usually worse on getting out of bed and on moving the affected part after it has been at rest for some time, and are somewhat relieved by rest and warmth. In some cases a periarthritides of the knee- or ankle-joint supervenes and may cause considerable disablement, which does not clear up for months or years. Dengue pains persist in the small muscles of the hands and soles of the feet, probably located to the deep fascia. They eventually wear off. Complications are few. Albuminuria, parotitis, orchitis, herpes labialis and epistaxis have been recorded.

Convalescence may be much delayed by anorexia, general debility, mental depression, sleeplessness, evanescent feverish attacks, boils and urticarial, lichenoid and papular eruptions.

In Europeans an attack of dengue very often leads to a condition of debility, necessitating temporary change of climate, or even return to Europe.

Variability of epidemic type.—Judging from the published descriptions, there is considerable variety in the symptoms of this disease in different places and in different epidemics. Some authors mention swelling and redness of one or more joints as a common and prominent symptom; others refer to metastases of the pains, enlargement of submaxillary glands, general adenitis, mental depression, hæmorrhages, and so forth. However this may be, the essential symptoms in well-marked cases are the same practically everywhere and in all epidemics, viz., suddenness of the rise of temperature, an initial stage of skin congestion, limb and joint pains, and a terminal rubeoloid eruption.

As there are varieties or strains of every virus known it is highly probable there are different antigenic strains of dengue virus. This, as in the case of influenza, would account for the frequency with which persons who have had dengue more than once in one area go down immediately on going to live in another dengue area.

Relapses are not uncommon in dengue, and second and even third attacks have been recorded. As a rule, however, susceptibility is exhausted by one attack.

Immunity.—Schule pointed out that certain of his volunteer American soldiers proved remarkably resistant to experimental inoculation with the dengue virus, and these were individuals who had been resident for some time in an epidemic area of the disease. Probably, immunity is due to previous mild attacks. The immunity in dengue does not last more than six months; it thus differs from that of yellow fever, which is life-long.

Mortality.—In uncomplicated dengue the mortality may be said to be almost nil (0·1 per cent., Hare). During the 1928 epidemic in Greece Cardamitis gave the mortality-rate as 1 in 61,000.

Diagnosis.—Dengue must not be confounded with yellow fever, Rift Valley fever, rubeola, scarlatina, measles, Colorado tick fever, Bullis fever, syphilitic roseola, influenza, cerebro-spinal meningitis, typhus, hæmorrhagic smallpox, enteric, phlebotomus fever, seven-day fever (leptospirosis).

rheumatic or malarial fever. A knowledge of the distinctive features of these diseases, and the fact that dengue is attended with a rash and with articular pains, and that it occurs in great and rapidly spreading epidemics, should prevent any serious error. A complement-fixation test has been devised (Sabin and Young). The antigen is extracted with benzene from the brains of 8-14 day old mice inoculated intracerebrally with a dengue virus exalted in virulence by repeated passages through baby mice.

Using this antigen, complement-fixation titres of 1 : 64 to 1 : 256 were obtained in human volunteers within 2-6 weeks of inoculation, and also in rhesus monkeys and chimpanzees injected with homologous strains of the virus. Within six months reaction became negative.

Recently, the hæmagglutination test has proved useful. Nakagawa and Shingu (1956) recovered a specific hæmagglutinin from a 2-4 day-old mouse brain infected with dengue virus. This hæmagglutination with dengue virus was inhibited by hyperimmune mouse and rabbit sera.

Treatment.—Were it possible to secure perfect isolation and immunity from mosquito-bite for the individual during an epidemic of dengue, doubtless he would escape the disease. Even comparative isolation is attended with diminished liability. There is no specific treatment.

Like the allied fevers, dengue runs a definite course; therefore it is useless to attempt to cut it short. The patient should go to bed as soon as he feels ill, and should keep to his room until the terminal eruption has quite disappeared and he feels well again. Ten days is not too long to allow in severe attacks. As in influenza, light liquid diet, rest, and the avoidance of chill conduce powerfully to a speedy and sound convalescence. At the outset of the fever some saline diaphoretic mixture, with aconite, may be prescribed with advantage. If the pains be severe and the fever high, antipyrin, phenacetin, belladonna, or vinum colchici (15 min. t.d.s.) give great relief. Cold applications to the head are comforting. If the temperature rises to 105° F. or over, cold sponging or the cold bath ought to be used.

Prophylaxis is the same as for yellow fever and for other mosquito-borne diseases, and is directed against infected mosquitoes.

Prophylactic inoculation.—St. John and Holt attempted to produce a dengue vaccine. Vaccine made from the liver and spleen of dengue-infected monkeys did not protect volunteers from an attack; but there was evidence that the disease became mitigated in the inoculated. Hotta (1958), in tests on human volunteers, found that formolized vaccines were inactive, but that bile-treated vaccines had a protective value.

CHAPTER XXII

COLORADO TICK FEVER, BULLIS, EPIDEMIC HÆMORRHAGIC AND IZUMI FEVERS

IN 1930 Becker described a disease called Colorado tick fever which up to that time had been assumed to be a mild form of Rocky Mountain spotted fever. The disease is associated with the bite of the wood tick, *Dermacentor andersoni*, but evidence that infection is transmitted by the tick is largely circumstantial. The virus will pass through a membrane of pore size $24\text{ }\mu$, and is thus one of the smaller viruses. The incubation period is four to six days and there is usually a sudden onset with chilly sensations, generalized aching, headache, post-ocular pain and lumbar backache. A temperature of between 102° and 104° F. is usually attained within twenty-four hours and is associated with an increased pulse rate. This attack lasts two days and is followed by a symptom-free interval of the same duration with a subnormal temperature. The second attack lasts about as long as the first or a day longer and may be more or less severe than the first. Single or triple attacks have been reported, but are rare. Apart from a mild erythema and slight conjunctival injection there are no physical signs and complications and death have not been recorded. There is a leucopenia involving all white cells except the monocytes. Colorado tick fever is not unlike Rocky Mountain spotted fever and dengue, but those who are immune to Rocky Mountain fever and dengue can be inoculated with Colorado tick fever.

BULLIS FEVER (LONE STAR FEVER¹)

A new form of fever appeared in Texas in the spring and summer of 1942 in soldiers engaged in field exercises at Camp Bullis, near Houston, Texas. All patients had multiple tick bites by *Amblyomma americanum* shortly before the onset. The fever lasted from 3 to 13 days in a series of 33 cases. The onset was abrupt, with post-orbital and occipital headache, and the fall of fever was by lysis. General adenopathy was common. In the more severe attacks, a maculo-papular rash appeared on the trunk, in some resembling murine typhus, in others like German measles; it never lasted more than 48 hours. On the second or third day there was pronounced leucopenia, with associated neutropenia (Woodland, McDowell and Richards, 1943). Later, Anigstein and Bader (1943) isolated, from a collection of *Amblyomma americanum*, a virus which was established in guinea-pigs.

EPIDEMIC HÆMORRHAGIC FEVER

Synonyms "Red fever of Korea," Songo fever, Kokka disease, Korin fever, Nidoko disease: names reminiscent of places where some of the earlier outbreaks have occurred. The fever resembled "scrub typhus" in its epidemiology, but the clinical features differed considerably. It was known to the Russians in the basin of the Amur river and in Manchuria in 1938, and to the Japanese in Korea towards the close of the Second World War. Cases had been reported in Japanese medical literature and known as hæmorrhagic nephroso-nephritis. It is generally considered to be a virus disease transmitted to man by the mite—*Laelaps jettmari*, Vitzthum. The host of this mite and probably also the reservoir of the virus is a field mouse—*Apodemus agrarius*.

In clinical features it presents considerable differences from the typhus group. The disease is characterized by fever, myalgia, albuminuria and a petechial rash. In more severe cases hæmoptysis, hæmatemesis, hæmaturia, and melaena

¹ *A. americanum* is popularly known as the "Lone Star tick" from the bright spot on the scutellum of the female tick.

may occur. The onset is usually abrupt. Conjunctival hæmorrhages are frequent, except in the first three days, but the pain and photophobia lead the patient to close the eyes or to shade them, whilst the slight œdema of the upper lids gives the patient a bleary-eyed appearance, resembling measles without lachrymation. Retro-orbital pain, backache, severe anorexia, nausea and emesis suggest the diagnosis. The intense erythematous blush of the face and neck are due to toxicity, whilst the conjunctival and pharyngeal injection are out of proportion to any pharyngeal symptoms. The pulse is rapid and blood-pressure may be imperceptible. Death is due to peripheral vascular collapse. The urinary findings closely resemble those of acute glomerular nephritis. The tubular injury results in varying degrees of oliguria which can be accounted for by anoxia. Albuminuria is associated with large numbers of oval bodies in the urine which represent mononuclear cells and renal tubular cells (Ganong). These changes are primarily due to capillary fragility. Albuminuria, 1-4 plus, appears from 28-72 hours from the onset and persists for one week. The specific gravity falls to 1005. Pathological changes consist of œdema, congestion and hæmorrhages. These phenomena are most conspicuous in the anterior pituitary, kidneys and R atrium of the heart. The kidneys are so considerably involved as to be diagnostic. The cortex is sharply demarcated from the medulla, where hæmorrhages and a peculiar type of necrosis are present. Fever usually lasts about seven days and in favourable cases there may be complete recovery within fourteen days of onset, but in others a low-grade fever, palpitations, insomnia and anorexia may persist for some weeks. The fatality rate in Japanese hands was about 13 per cent. The fever has a seasonal incidence and is most frequent in May, June, October and November.

Treatment is symptomatic. Antibiotics and sulphonamides are ineffective. Transfusion of blood from convalescents appears to shorten the duration of the fever. Fluids of any kind, oral or intravenous, must be given in small amounts, because of increased capillary permeability. They increase the œdema. The maximum amount should be that of the urinary output, plus 500 ml. to cover insensible loss.

Epidemic hæmorrhagic fever has to be differentiated from relapsing fever, purpura, leptospirosis and typhus. In Russia what is known as alimentary toxic aleukia is due to eating diseased grain infected with the fungus, *Fusarium sporotrichoides*. Other hæmorrhagic fevers are *Crimean*, said to be transmitted by the tick, *Hyalomma marginatum*, and it is suggested that the reservoir might be the hare; *Omsk* hæmorrhagic fever is carried by the tick *Dermacentor pictus*, but both of these fevers do not develop nephritic complications. Hæmorrhagic fever in Bukovina is transmitted by *Ixodes ricinus* and is probably the same as the foregoing. Others from Uzbekistan and Turkmenistan resemble this epidemic hæmorrhagic disease very closely.

Prophylaxis.—Should the Japanese account of the ætiology be correct this should be the same as that for mite or "scrub" typhus.

IZUMI FEVER (Japan)

Since Prof. Izumi first described a sudden outbreak of a scarlatina-like disease in the town of Kanagawa in 1927, over one hundred outbreaks have been reported. It is now recognized as constituting an independent disease in its clinical aspects, though the specific cause has not yet been ascertained.

Nishioka and Morita (1952) have studied a sudden outbreak in a fishing village in the Sakishima district of the Shima peninsula, S. of Tokyo, in 1951, where epidemiological investigations revealed that it was due to drinking spring water. This fever occurs both sporadically and in epidemics. Secondary, or case-to-case, infections are very uncommon.

CHAPTER XXIII

PHLEBOTOMUS FEVER

Synonyms. Papataci Fever; Three-day Fever of Chitral (McCarrison); Sandfly Fever, "Dog Disease," "Hundfieher," "Russian Headache Fever," Bessarabia Fever (Boehnhardt).

Definition.—A specific fever of short duration and no mortality caused by a virus introduced by the bite of a sandfly (*Phlebotomus*).

Geographical and seasonal distribution.—Sandfly fever is coextensive with that of insect transmitter (*Phlebotomus*). Absent in Bermuda where no sandflies are found. In tropics it occurs as epidemics amongst new arrivals; sometimes 75 per cent. are attacked. Natives of endemic areas appear to be immune. In subtropics it principally occurs during summer and autumn. Sandfly fever was common in wars of 1914–1918, 1939–1945 in Mediterranean—Malta, Gallipoli, Aegean islands, and in Yugoslavia. Widespread in Egypt, Sudan, Palestine, Syria, Iraq, Persia and India, S. China. Common in Africa with exception of W. and E. Africa; Red Sea provinces, Arabia, and Persian Gulf. In America, N. Argentine, N. Brazil, Panama and some West Indian islands. In Caucasus, Chitral and Himalayas it is found up to 4,000 ft.

Epidemiology.—In Palestine and Syria spring and autumn outbreaks are common. In Malta the peak period is in July, falling gradually to the second week in November. Two waves occur, each lasting 3–4 weeks. The first at commencement of the hot weather, the second in the autumn, being due to the second brood of sandflies. The eight weeks between the epidemic peaks is the approximate time required by *P. papatasi* to complete its life cycle. In Yugoslavia, Guelmino and Jevtić (1955) found that repeated attacks were associated with a high rate of prevalence of sandflies from June to September. About three-quarters of the population were attacked. A succession of four dry and hot years favoured the prevalence of these insects.

Ætiology.—The virus resides in the patient's blood during the first two days of the fever. It is ultramicroscopic, passing through filters which arrest *Brucella melitensis*. According to Doerr, the virus may be transmitted hereditarily through the egg and larva of phlebotomus to the imago, and this has been confirmed by Mochkovski and Diomina. The infection is transmitted by the bite of female sandflies of the second generation hatched from eggs laid 6–8 days after the infecting feed. Infection has been produced by the bites of newly-hatched sandflies. A short sharp fever has been produced in monkeys after intravenous injection of sandfly-fever blood. Little is yet known of the physical properties of the virus. According to Whittingham, it may survive the winter, either free in the soil, or within the bodies of phlebotomus larvæ, which inhabit such sites as moist soil and porous walls. If this is correct, then it is the only instance in which an animal virus has been transmitted hereditarily by an insect

vector, but may be an important epidemiological consideration and explain the suddenness and extent of outbreaks of sandfly fever in India and North Africa in the spring.

Shortt, Poole and Stephens showed that, as with dengue, the sandfly-fever virus can pass through L_3 and L_6 Chamberland filters, and that it is present in the highest concentration in the blood during the first and second day of the disease. They proved that it can survive outside the body for sixty hours. Shortt, Pandit, Anderson and Rao cultured the virus on the chorio-allantoic membrane of the chick embryo; by subsequent inoculation it could be demonstrated in monkeys for an average of 11 days, and subsequently immune bodies up to 69 days. According to Russian workers the virus causes a proliferative necrosis of the chorio-allantois. It can be inactivated by treatment with commercial formalin, 1 in 1000, and it can be dried and preserved in a vacuum desiccator for eight months.

In cases of fever and in convalescents the presence of the virus in the blood can be demonstrated by egg-culture up to three or four weeks from the onset of fever.

Representatives of the genus *Phlebotomus* are to be found in most tropical and subtropical countries. The various species are usually designated "sandflies." They are exceedingly minute, very delicate, greyish, or brownish, somewhat slenderly-built insects that bite principally during the night and that can pass easily through the meshes of an ordinary mosquito-net. The powers of flight are feeble; more usually the insects progress by a series of short skips.

It must be emphasized that not all species of phlebotomus transmit the disease, only, as far as is known, *P. papatasi*. There are many species of sandfly in Africa in places where there is no sandfly fever.

P. papatasi, the species on which Doerr's observations were made (hence one of the names for the disease, papataci fever), lays about forty eggs, selecting for the purpose damp localities such as the walls of cellars, of latrines, cesspools, crevices in walls, caves, and embankments. The cycle of egg, larva and imago takes about one month in warm and upwards of two months in cooler weather (see pp. 1034-1036). It has not been determined which of the many species of phlebotomus, other than *P. papatasi*, conveys this fever. The insect can transmit the infection after an incubation period of six days.

Pathology.—Dengue and phlebotomus fever have several important points in common, a circumstance suggesting the possibility of a common or, at all events, a similar origin. Each is transmitted by an insect; the viruses occur in the blood-stream and are filterable; they are diseases of warm climates only; and clinically, they are characterized by a short incubation period and a brief and rapidly developed fever which is usually associated with relatively slow pulse and leucopenia, and relative decrease of the polymorphonuclears. There is no evidence that these diseases are mutually protective. The post-mortem appearances of sandfly fever are unknown.

Symptoms.—The bites of the infected sandfly occasion a considerable amount of irritation, resulting in hyperæmia and even in œdema. After an incubation period of from four to seven days, with or without a prodromal stage, the fever is ushered in suddenly by slight or more severe rigor with a temperature of 102° F. which may reach 105° F. In 10 per cent. there is a short secondary rise. The face becomes flushed and swollen, frontal

PHLEBOTOMUS FEVER

headache is intense, and there is usually severe general aching and stiffness in the back of the neck. Agonizing photophobia, accentuated by pressure on the globes or by the least movement of the head, is characteristic. Supraorbital headache is also quite common. There are influenzal pains in the back and legs and general stiffness of the muscles. More rarely the pain is referred to the epigastrium. A sense of band-like constriction round the lower part of the thorax is sometimes so prominent as to resemble epidemic pleurodynia, or Bornholm disease. The patient is drowsy, but suffers from insomnia. The conjunctivæ are so injected that the eyes have been compared to those of a mastiff. The tongue has a central fur. The

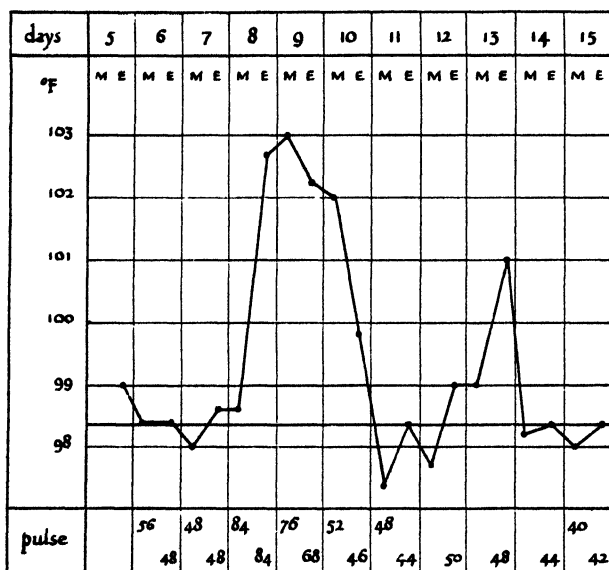


Chart 21.—Phlebotomus fever showing prodromal period, typical attack, recrudescence and bradycardia. (Lambert, *Jl. Roy. Nav. Med. Ser.*)

fauces and palate are often congested, and are studded with small vesicles ; it has been remarked that they are devoid of any surrounding mucosal inflammation. The vesicles are not strictly peculiar to sandfly fever as they have also been noted in infective hepatitis. In from twenty-four to thirty-six hours the temperature has reached 103–104° F. (Chart 21). It keeps about this point for a day longer, and then begins to fall, with or without epistaxis, vomiting, sweating and diarrhœa, reaching the normal about the end of the third or beginning of the fourth day. The patient continues debilitated, especially mentally, for a week or two longer. The name “three-day fever,” applied to the disease, is misleading, since the pyrexial period may occasionally vary from two to eight days. In some cases there are several days of apyrexia followed by a secondary rise of temperature lasting a day or two.

The blood-picture shows a slight leucopenia, without serious alteration in the proportion of mononuclears, especially from the second to fourth day, after which there is a leucocytosis of 15,000–20,000. The pulse-rate is relatively slow. Relative bradycardia is noticeable by the second day of the disease, as soon as the patient complains of headache, and is possibly due to increased pressure of the cerebro-spinal fluid. An absolute bradycardia is noted at the end of the fever.

Le Gac and Albrand first recorded that the cerebro-spinal fluid is under increased pressure and that it contains from 10 to 110 lymphocytes per cu.mm. Albumin is always increased and the chlorides slightly decreased. These findings have been amply confirmed.

Shee (1942) described varying degrees of choking of the optic disc, ranging from blurring of the edges to papilloedema. This was seen in the early stages, but in severe cases was visible at the crisis.

No serious complications occur, but in some years diarrhoea, in others pharyngitis, are features of the disease. Constipation, vomiting and stiffness of the muscles at the back of the neck are not uncommon. Second attacks are by no means rare, but are milder, and third and fourth attacks have been recorded. Shortt proved that immunity may sometimes persist for one year after an attack. On the whole, children suffer less severely than adults. It is hardly necessary to state the importance of distinguishing sandfly fever from abortive cases of acute poliomyelitis which may occur sporadically in sandfly fever districts.

Pearson (1941) drew attention to the similarity of benign lymphocytic meningitis and sandfly fever. There seemed to be in Palestine some connection between the incidence curve of the two. The cardinal signs of sandfly fever—frontal headache, orbital pain, photophobia, pains in the back, fever and conjunctival congestion—are duplicated in benign lymphocytic meningitis. The debility which ensues in some individuals is quite out of proportion to the intensity and duration of the initial attack. Acute synovitis as a complication has been observed in Iraq during the recent war. The mortality is nil.

Attention has quite recently been drawn to a dermatitis, known as "Harara" (i.e. heat), which is common in Anatolia, Syria and Palestine during the sandfly season, and is a reaction due to their bites. It is also stated that infected sandfly bites are the most painful.

Immunity is short-lived and second attacks occur in about 10 per cent., third attacks in 0·8 per cent. Certain individuals may suffer from several attacks in the same epidemic. There appears to be a high degree of immunity in the inhabitants of endemic areas.

Sandfly fever nets are of such small mesh that they are insufferably hot, and in Malta during the 1939–1945 war were replaced effectively by wide mesh nets impregnated with DDT.

Diagnosis.—It is extremely difficult in the early stages to distinguish this fever on clinical grounds from malaria (especially subtertian), from paratyphoid, dengue, typhus and influenza. In typhus the greater hebetude, and in influenza the respiratory catarrh, must be taken into consideration.

In Syria during the last war years there was often some difficulty in distinguishing between the prodromal stage of infective hepatitis and sandfly fever.

Treatment.—The most valuable drug in the treatment of sandfly fever is opium; 30 drops of the liquor opii sedativus may be given at the onset. It greatly relieves the headache. Quinine is useless. Tincture of iodine should be applied to the bite. The headache has been relieved by lumbar puncture and removal of 5 ml. of fluid. Whenever possible, patients should be nursed under sandfly nets.

Prophylaxis.—As phlebotomus fever appears to be a disease of locality, houses and places believed to be infected should be avoided and, where possible, disinfected.

To diminish the local sandfly pest, all rubbish should be burned or otherwise got rid of, ruinous walls demolished, cracks in walls filled in with tar or mortar, latrines smoked with sulphur fumes, put into sanitary condition, and dark damp places dried, whitewashed, and ventilated. No gardens or cultivated ground should be permitted in the immediate vicinity of buildings. Creepers should not be allowed to grow on barrack walls. Benzene polychlorines, widely used in agriculture, are useful for destruction of sandfly larvæ, and are applied in solution in the strength of 75 ml. to every square metre. The adult flies can be killed in numbers by "swatting." By these and similar measures much can be done to control the infection. Unfortunately, a net having a mesh sufficiently small (i.e., 45 holes to the inch) to keep out sandflies is intolerable to a white man in a hot climate. As the phlebotomus does not fly higher than 10 ft., removal to an upper story is a very effectual preventive measure. *Flit* and DDT are the best sprays for destroying adult sandflies. Special staffs are necessary for the daily destruction of these insects in dwellings (*see* p. 860). Dimethyl phthalate is the best repellent (*see* p. 284).

Shortt and his colleagues used the cultural virus as a vaccine. In inoculated volunteers immune bodies in the serum were subsequently demonstrated.

CHAPTER XXIV

THE POCK DISEASES

At the present time classical smallpox is largely restricted to tropical and subtropical countries, where the preventive measures responsible for the decline of this disease in temperate climates are more difficult to enforce. In India and Pakistan, for example, the number of cases of variola reported during the year 1938 was 82,640, with a mortality of 27 per cent. There have been severe outbreaks in China (Hong Kong and Shanghai) and in Nigeria; and a mild form of the disease with no fatalities has been prevalent in the southern states of the United States. India remains the world's chief reservoir.

During the last few years much has been learnt about the nature and properties of the causal agents of the pock diseases. The greater part of this work has been carried out with vaccinia, and it is therefore necessary to define at the outset the relationship between this virus and variola. That smallpox and all the animal pock diseases are closely related is certain. There are two possibilities: (1) a primitive mammalian pox has given rise to variola and alastrim in man, cow, horse, camel, sheep, goat and rabbit pox and also the disease of mice known as ectromelia, or (2) human pox has infected man's domestic animals or those animals closely associated with man giving rise to specific varieties of pox. Van Rooyen and Rhodes suggest that variola, vaccinia and the cowpox group, mutually protective, contain a group, and a highly specific (variolar), antigen. Therefore variola degenerates into vaccinia when the latter antigen is lost on animal passage. Human pox and that of the horse, sheep, goat, and possibly camel, can be adapted to the calf giving rise to vaccinia variants. All the vaccinia strains now used for immunization are derived from variola, either through the calf or sheep, or by inoculation into monkeys and thence on to rabbits. Vaccinia derived from variola is more virulent for the rabbit and calf than for man, while variola is more virulent for man than for the rabbit or calf. There is no close relationship between vaccinia and true cow-pox, which latter disease can be transmitted to persons immune to vaccinia. The transition from variola to vaccinia is, fortunately, not reversible, so that once a strain of virus has been adapted to the calf or sheep it can be inoculated into man, producing in him a mild illness which renders him subsequently immune to the virulent parent form—smallpox. On rare occasions vaccination gives rise to a generalized papular or vesicular eruption with severe constitutional symptoms which may terminate fatally. This condition is believed to be due to an abnormal susceptibility to vaccinia, and not to an increase in virulence of the virus.

SMALLPOX (VARIOLA)

Ætiology.—The infective agent of vaccinia is a round body, measuring about 170 to 250 $m\mu$ in diameter, to which the noncommittal term "elementary body" is applied pending the settlement by further research of the much-disputed

question whether viruses should be regarded as micro-organisms or macromolecules. These bodies were first seen and described in 1887 by Dr. John Buist of Edinburgh, who found them in the vesicle fluid of smallpox and vaccinia. In 1892 Guarnieri described corpuscles and elementary bodies. In 1906 they were rediscovered by Paschen and are frequently referred to as "Paschen bodies." It is only during the last few years, however, that the bodies have been proved to be the casual agents. Methods have now been evolved of preparing pure suspensions of the elementary bodies from the skin lesions produced in rabbits and sheep by specially-selected strains of vaccinia virus. These pure suspensions have been employed in recent studies of the physical, chemical and biological properties of the virus, and they are also being used experimentally in place of crude lymph for prophylactic immunization against smallpox. Although the size of the bodies is below the limit of optical resolution for visible light, they can readily be seen with the dark-ground microscope. When stained, a central spherical mass is seen lying eccentrically and surrounded by a clear area in turn encircled by a number of small granules and very small intracellular bodies $0.1-0.25\mu$ in diameter which are now known as Paschen's bodies. The smallpox virus has been recovered from cutaneous lesions in every stage and its powers of persistence have been demonstrated by egg cultivation from crust material after months of separation from the host. A patient is infectious from the appearance of the first blemish until the last scab has separated.

When inoculated by inunction into the skin, the elementary bodies penetrate the cytoplasm of the epidermal cells and there proceed to increase in number, thus producing, perhaps with the addition of material derived from the infected cell, the so-called acidophil inclusion body which was described long ago by Guarnieri. The virus within the cells causes them to increase in size and also to proliferate freely. This increase in thickness of the epidermis, together with oedema and hyperæmia of the subjacent dermis, is responsible for the papule. Later, the cells forming the centre of the papule degenerate and liquefy, thus producing the characteristic vesicle, in the fluid contents of which the elementary bodies are found in enormous numbers. The vesicle is rapidly converted into a pustule by the immigration of inflammatory cells, mainly polymorphonuclears, derived from the dermis. The fluid provides an excellent culture medium for staphylococci and other organisms, and the leucocytic response is largely due to this secondary infection. In non-fatal cases the crusts or scabs, which separate after the pustule has dried, contain active virus. The high infectivity of smallpox, however, is probably not due to dissemination of the crusts, but to lesions present in the mouth, throat and lungs and to droplet infection.

Vaccinia and variola, in common with other viruses, cannot be cultivated in the absence of living susceptible cells. The virus can be grown readily in tissue cultures of rabbit testis or corneal epithelium, and proliferation also takes place in a fluid medium consisting of rabbit serum and Tyrode's solution to which small amounts of minced rabbit kidney or testis have been added. Vaccinia also grows without difficulty when implanted on the chorio-allantoic membrane or yolk sac of the developing chick embryo with material obtained from the second to fourth day of the disease. Both these methods have been used successfully to procure a supply of bacteria-free virus material for prophylactic immunization. This culture virus may be inoculated by scarification in the usual way, or it may be injected intracutaneously. The latter method has the advantage of leaving no scar, but since a vaccination scar is the one infallible sign that a person has been immunized against smallpox, it would increase the difficulties of controlling an epidemic, especially among coloured races. There is evidence that strains which have been grown *in vitro*, or on the egg membrane for a long time, become attenuated so that they may fail to induce a good immunity when inocu-

lated into man. Generalized vaccinia has been known to occur as the result of vaccination with virus grown on the chick embryo, and in addition the danger of sensitivity to egg proteins must be remembered.

Diagnosis.—Difficulties in diagnosis are due to:—

- (a) resemblance to chicken-pox
- (b) occurrence of mild cases.

In smallpox prostration is severe. Spots, when charted, show that larger numbers are centrifugal: in chicken-pox centripetal—a reliable early sign.

Depth of spots.—In chicken-pox they are superficial. In smallpox they are deeper and often “spotty.” In chicken-pox the spots may be elliptical or oval and fresh crops occur on several successive days. Vesiculation and crusting of papules occurs very early, within two days. Initial rashes may simulate scarlet fever, rubella or measles. Rarely to be differentiated from hæmorrhagic scarlet fever and measles, typhus and other erythematæ. The true rash has to be distinguished from chicken-pox, rickettsial pox, plague, drug eruptions, especially with potassium iodide.

Paul's test is widely used and consists of diluting liquid contents of a vesicle which is placed on the scarified surface of a rabbit's cornea. In 48 hours small elevations appear on the inoculated eye. On microscopical examination of excised cornea, Guarnieri's bodies are present. This test is negative in chicken-pox.

Laboratory diagnosis.—Elementary bodies can readily be demonstrated in the vesicle fluid by the dark-ground microscope. Van Rooyen and Illingworth (1944), however, confirmed Paschen's observation that the elementary bodies of variola are larger than those of varicella, and are easily demonstrated in the papular and vesicular stages. They have utilized this finding to form the basis of a laboratory test for smallpox. The technique is the same as that for the detection of spirochætes. Permanent preparations are best prepared by using Gutstein's method:

Solutions needed.—(a) 1 per cent. methyl violet in distilled water.

(b) 2 per cent. NaHCO_3 .

Technique.—A drop of the vesicle fluid is spread on a perfectly clean microscopic slide as for a blood film. It is dried in the air, or in an incubator, and rinsed in physiological saline and then with distilled water. When dried, the film is fixed in methyl alcohol (or ethyl alcohol) for half an hour or more and put into a dry Petri dish. Equal parts of solutions (a) and (b) are mixed in a test tube, filtered at once on to the slide, covered with a lid and incubated at 37° C. for twenty to thirty minutes. Rinsed in distilled water, it is dried and mounted in cedarwood oil or liquid paraffin. The elementary bodies are stained distinctly and intensely a light violet colour.

Finding elementary bodies in the vesicle fluid is of no value in differentiating smallpox from varicella, since the infective agent of the latter disease also takes the form of elementary bodies, and the two viruses are indistinguishable under the microscope.

The best methods for the diagnosis of smallpox are: (1) complement fixation, using a suspension of the crusts as antigen, and (2) implantation of smallpox virus on the chorio-allantoic membrane of the developing chick embryo. The first test takes 24 hours, the second three days. Downie's flocculation test is also widely employed.

The serum of a patient who is recovering from an attack of smallpox contains agglutinins which react specifically with variola elementary bodies. These antibodies are not present in detectable amounts until the second week of the disease, and the reaction is therefore of little diagnostic value.

In animals and rabbits inoculated with cultivated virus a red swelling appears on the second day, reaching its maximum on the fourth and disappearing in twelve days.

Serological methods have so far failed to discover any antigenic difference between *variola major* and *variola minor*. It is thus evident that the diagnosis of smallpox must be made mainly by clinical methods, but that laboratory tests may be of use in doubtful cases.

THE TECHNIQUE OF VACCINATION

In performing vaccinations in the tropics it is important to remember that exposure of the recently vaccinated arm to the rays of the sun rapidly inactivates the virus. Persons who have been vaccinated should be kept in the shade for at least half an hour and should be watched to see that they do not remove the vaccinia by licking or sucking the scarified area. A lesion closely resembling a vaccination is made by rubbing in the juice of the cachou nut into a lightly scarified area. Immunity is established on the ninth day after vaccination. General experience shows that successful vaccination within 24 hours of first contact is protective.

In recording the results of vaccination a redness coming on in from 24 to 48 hours after vaccination with itching must not be taken as a reaction of immunity. It may be caused by killed vaccine or by sensitivity to proteins in the vaccine. The only positive reaction is a distinct raised papule coming on in three or four days after vaccination and, if possible, going on to a pustule. If an allergic reaction alone is produced, vaccination should be repeated in a fortnight's time, preferably with a different batch of vaccine. Vaccine virus should be kept in the cold. Vaccinal encephalomyelitis is rare in the tropics, but cases have been recorded.

The clinical picture.—The incubation period is 14 days and that it is any longer in alastrim has not been confirmed. Smallpox is a diphasic illness. The *toxæmic* phase lasts one week and is a true virus illness. The toxæmic prodromal rash is erythematous and has a predilection for the groins, axillæ and flanks. The rash may be scarlatiniform, or morbilliform, which may be confined to "bathing drawers area." The temperature may be 103° F. on the first day. The pulse is rapid: tongue sore, *restlessness*, often delirium and prostration may be severe. The *second* stage is dominated by a focal rash and the severity of the illness is determined by the number and severity of the eruptions, especially on the face. The focal lesion outcrop begins on the third day. The whole period of the development of the pustule occupies about eight days.

Formation of the pock.—Degeneration occurs in the Malpighian layer of the skin. They liquefy and lymph exudes producing a vesicle which is *multilocular* owing to the persistence of trabecullæ. *Umbilication* is due to changes being more advanced at the periphery.

Discrete form.—The eruption appears on the third day on the forehead, back of the wrists and hands and very often in the mouth and fauces. The spots are circular in shape. Rash spreads on face, trunk, and extremities. Lastly it appears on the soles and palms in one crop. In appearance it is successively macule, vesicle, pustule and crust. In the early stages, the spots are *bright red macules*, 1/10 in. in diameter which disappear on pressure, becoming in a few hours *papular*. On fifth or sixth days *vesicles* form with clear summits. They are *umbilicated* and 1/2 in. in diameter. On the eighth day they become pustular and opaque. The umbilication disappears. Maturation commences on the face and spreads.

Ricketts (1908) first explained the disposition of the focal lesions in relation to the surfaces of the body. As a rule the rash is set more thickly upon the uncovered and vascular face and the mobile limbs, than upon the relatively fixed trunk. They are less in flexures such as the axillæ and flexor surfaces.

Symptoms.—With the appearance of the rash the temperature and the severe symptoms subside till about the 8th day when the *secondary* fever returns with itching, swelling and *painful* skin. The eyelids are swollen and closed; mouth dry and deglutition painful; thirst extreme. Delirium may be slight or absent. About the tenth day pustules commence to rupture and pus exudes. Scabbing continues during the third and fourth weeks. The resulting pitting may be slight. In the *confluent form* the pocks coalesce and the initial symptoms are usually more severe. On the eighth day the pustules form and coalesce and large superficial abscesses result. The temperature is high, pulse rapid, thirst is marked and delirium is frequent. The pustules break and exude pus or may desiccate unruptured. Scabbing occurs in the third and fourth weeks. Pitting is very severe especially on the face.

Hæmorrhagic smallpox occurs in two forms. (1) Black smallpox or purpura variolosa and (2) Hæmorrhagic pustular smallpox.

Purpura variolosa is most common in adult males and rare in children. It is always severe. The eruption appears on the 2nd to 4th days and is petechial from the onset. Often commences in the groins and accompanied by hæmorrhages from the mucous membranes with hæmaturia, hæmoptysis and hæmatemesis.

Hæmorrhagic pustular smallpox.—The hæmorrhages commence in vesicular and pustular stages. The earlier the onset, the more severe the condition. Death occurs on seventh to ninth days. Recovery is exceptional.

Complications are bronchopneumonia which is present in all fatal cases, laryngitis from œdema of the glottis or necrosis of cartilages. Conjunctivitis is common, *keratitis* in the confluent form and may lead to blindness. Septicæmia is often seen in the pustular stages. Boils and abscesses are very frequent and troublesome. *Osteomyelitis variolosa* destroys the epiphysial lines in growing bones and produces defective growth.

Varioloid is the modified form occurring in vaccinated persons, when there is resistance to the virulence of the infecting agent. The onset is usually abrupt, though the *initial symptoms* may be severe as in other forms, but the rash appears as papules on the third or fourth day, when the temperature and symptoms subside. The stages of vesicle and pustule are short and no secondary fever supervenes. Pitting is very rare—within five years of vaccination, varioloid is rarely severe.

The really important thing is that varioloid should be recognized as such, mainly because these cases are infectious to others and virulent types of the disease may occur. Sometimes vaccinated subjects, when infected at an early stage of waning immunity, may react with a high feverish illness which is known as *variola sine eruptione*, or contact fever. The infectivity of this condition is doubtful.

SUMMARY OF SMALLPOX

Incubation period 12–14 days.

The patient should be isolated until all scabs have separated, leaving dry, healed pocks.

Contacts.—A person protected by vaccination should be kept under daily observation for 16 days. If not so protected he should be in quarantine for 16 days.

Initial Symptoms.—Almost always a severe onset resembling that of any

acute illness, e.g., influenza, pneumonia, rheumatism, meningitis, malaria, dengue, etc.

Backache is a very common but is not always present. Pain may even be referred. Cases have been mistaken for appendicitis where on operation a normal appendix has been found.

A high temperature up to 106° is common.

Mental symptoms in any case of suspected smallpox should be carefully watched. The patient may escape or commit suicide.

The temperature is at first a fever of toxæmia; after the rash appears it becomes one of suppuration.

Prodromal Period.—Lasts for 2–3 days. Two types of prodromal rash:

- (1) Erythematous.
- (2) Hæmorrhagic.

The *Erythematous type* has nothing definite, but resembles food rashes, German measles, scarlet fever, dengue, etc.

The *Hæmorrhagic type* is however different.

One variety, the “Bathing Drawers type,” is very characteristic and is seen chiefly in smallpox.

Facial expression is also characteristic. Due to paresis the lower jaw tends to drop.

The hæmorrhagic rash and facial expression may be mistaken for food poisoning or purpura hæmorrhagica.

Diagnosis.—Depends on:

Distribution of rash.

Character of focal lesions.

Distribution.—Broadly speaking the hollows and shallows of the surface tend to escape the rash at the expense of the ridges and prominences.

The most potent factors affecting the distribution are:

- (a) Exposure to air.
- (b) Friction due to movement, clothing, etc.

Exposure to air.—Face and hands. The incidence of the rash on these parts is greater than on any other part of the body.

Friction.—Of the three members—upper limb, lower limb and trunk—the first is the most mobile and most moved; it sustains the thickest rash.

The trunk is more constant, though in restricted motion; hence the leg is less susceptible than the trunk. The bulk of the rash is found on the back of the trunk, owing to more friction and movement. The flexure of the spine looks forward, nearly every movement therefore involving the dorsal arch causes friction with the underclothing. The eruption grows less, from the shoulders where it is thickest, down to the loins, and increases again over the buttocks as might be supposed.

The limbs have most mobility at their distal ends and the rash accordingly increases in density from above downwards.

The broad features of distribution are therefore that the rash prefers the upper half of the body to the lower, that it is a rash of the face and arms rather than of the trunk and legs, that it is a rash of the distal ends of the limbs rather than of the proximal, of the back of the trunk rather than of the front, of extensor surfaces rather than of flexor, and that it is a rash which shuns the most pronounced flexures.

The exceptions to the above are infants, invalids, and local irritation as from belts, garters, corsets, etc., where an abnormal distribution may occur.

Diagnosis is made on the character of the lesions.

Character of focal lesions.—A characteristic tendency of the rash is to shun the most sheltered parts of the cutaneous surface. These are the great flexures of

the body. The armpit enjoys an immunity which is virtually complete. The groins and hypogastrium less so. The rash is more marked on the extensor surfaces than on the flexor.

Eruption

Papular stage	2 days.
Vesicular stage	2 days.
Pustular stage	4 days.
Crusting or scabbing	8th or 9th day.
Pigmentation or staining	10th to 12th day.

The great bulk of the eruption is homogeneous, i.e., all are either papular, vesicular, pustular or crusts.

The Treatment of Variola.—In the modern treatment of smallpox isolation in special hospitals is imperative. At present there is no specific treatment. The patient must be nursed in bed, with a water-bed, if necessary. Nose and mouth must be swabbed frequently. Ice-cubes, when sucked, alleviate the pain and dryness of the mouth. For the initial symptoms opium is indicated: for vomiting, ice and *tinct opii*; for high fever, cold packs and hydrotherapy. For the *eruption* the hair should be cut short and for the face a lint mask is placed on the face and should be moistened with cold water and 2 per cent. carbolic solution. The itching parts are relieved by cold water, or by damp cloths covered with oiled silk. Directly the crusts form the skin must be allowed to dry. The best application for the face at this stage is a mask of thin linseed covered with vaseline.

Sulphonamides, such as sulphasuccidine in large doses, and penicillin injections, give good results by reducing sepsis and in combatting the secondary pyogenic infections of the respiratory tract. Continuous warm baths prove valuable and should be used on all with suppuration, confluent spots or toxæmia and to hasten the separation of crusts. Treatment of the eyes is of great importance. They should be bathed with boracic lotion and the edges of the eyelids smeared with vaseline. Delirium and sleeplessness should be treated with morphia or barbiturate sedatives. The treatment of smallpox with red light has been hallowed by time and custom and it is certainly true that the maturation of the spots is less when they are guarded from light. Convalescence is usually rapid, but boils, when they form, should be opened.

ALASTRIM

Synonyms.—Amaas; Kaffir milkpox; West Indian modified smallpox; parasmallpox; variola minor.

Definition.—This disease has been noted by many writers in the West Indies and South Africa.

The name is derived from the Spanish *alaster*, meaning to scatter or strew over (referring to the distribution of the rash). It is a disease of little or no mortality, and resembles smallpox in its mitigated form. Indeed, the individual case of this disease is clinically identical with a mild case of smallpox; they can only be distinguished one from the other in the mass.

Geographical distribution.—The disease has been recorded from the West Indies, South and Central America (especially Brazil), Africa, the Mediterranean area, and during the last 30 years from time to time in Great Britain. The most noteworthy epidemic was in Trinidad in 1902.

Epidemiology.—A striking difference between classical smallpox and alastrim is seen in the rate of progress through an unvaccinated community. Smallpox becomes rapidly epidemic, whereas alastrim can only be said to

"smoulder," alternately waxing and waning, but never attaining really epidemic proportions. This, no doubt, depends upon the infectivity of the two viruses. There appears to be no seasonal incidence.

The spread of alastrim is brought about by intimate contact and overcrowding.

Symptoms.—The incubation period averages about fourteen days; prodromal symptoms may or may not be present. When observed, they are those of an influenza headache, with generalized aches and pains. Severe headache, vomiting, and rigors, typical of the onset of smallpox, are rarely noted. The eruption commences usually on the third or fourth day, but in some cases there is a complete intermission of all symptoms, during which the patient may return to his duties under the impression that he has recovered from an attack of influenza; after the lapse of the quiescent period the eruption appears first on the face and palate, then on the hands and arms, and later on the lower extremities. Thus, in these cases there is a prodromal period of seven or eight days.

Individual lesions.—The papules can be palpated under the skin, even before they are visible. As a rule, the eruption appears in one crop, and closely resembles that of smallpox in every respect, any differences being due to the more superficial situation of the pathological process in the skin. The pock may be umbilicated, but collapses more completely on being punctured than does the smallpox vesicle, that is to say, it is less definitely multilocular. Drying or crusting begins at about the end of the first week, and crusts have usually fallen by the end of the second or third, at which period the patient is considered to be free from infection.

The rash naturally differs somewhat in appearance on a dark skin; the individual pustules, when ripe and full of pus, show as light creamy-coloured areas, in contrast to the dark purple of the surrounding inflammatory zone, and appear like pearls upon a dark background.

Distribution of the eruption.—This is identical with the distribution of the smallpox eruption, which is centrifugal, and it serves to distinguish alastrim from chickenpox, the rash of which has a centripetal distribution. As in smallpox, the most protected parts of the skin are most free from eruptions, i.e. axillæ, groins, and abdomen. The parts most affected are the face, scalp, shoulders, back, arms and legs. Any part which has been previously specially exposed to irritation is more profusely affected; thus, pocks are apt to cluster at the site of old burns or scars.

Confluent rashes may occur but, though the appearance of the patient is somewhat alarming, his general health appears to be but little disturbed. These cases may be associated with a considerable fever.

It has been noted by most writers on this subject that the fetor accompanying the rash of true smallpox is not present in alastrim.

Prodromal rashes are absent.

The mortality-rate is minimal; in the series recorded it is about 0.45 per cent. (Ribas and Moody).

Treatment is symptomatic only; patients should be isolated in a smallpox hospital or elsewhere.

Prophylaxis.—Vaccination offers the most efficient method of protection against this disease, as in smallpox. In spite of the mildness of alastrim, it is considered desirable at present to treat it as a form of smallpox, and not only to isolate patients but to vaccinate contacts.

Chickenpox may sometimes be severe in the tropics, owing to secondary bacterial infection. It should then be treated with penicillin or sulphonamides. It is far more commonly an adult than a childhood disease in tropical Africa.

TABLE V

DIFFERENTIAL TABLE

Smallpox

- (1) Rash most abundant on face and back, scanty on abdomen and chest.
- (2) More abundant on shoulders than on loins.
- (3) The rash found on limbs, generally on arms and is centrifugal.
- (4) Favours prominences and surfaces exposed to irritation.
- (5) Lesions deep-seated with infiltrated base, circular in outline, homogeneous in character, multilocular and indented.
- (6) Spots all appear together and are therefore at the same stage.

Chickenpox

- (1) Abdomen and chest covered as thickly as face. Abdomen and back covered.
- (2) Distribution indifferent.
- (3) Rash tends to avoid limbs: centripetal.
- (4) Behaves indifferently.
- (5) Lesions superficial and base not infiltrated. Lesions frequently have an irregular oval outline, are not homogeneous, and generally unilocular. Never indented.
- (6) Crops of spots appear so that lesions are at different stages.

Subsection F.—FEVERS DUE TO ATMOSPHERIC CAUSES

CHAPTER XXV

HEAT-HYPERPYREXIA, HEAT-EXHAUSTION AND SUN-STROKE

Preliminary.—In hard muscular work the heat production is great and, even when well trained, a man does not turn more than one-third of the energy generated into work, two-thirds being converted into heat. An ill-trained man, on the other hand, has an efficiency no higher than a steam-engine, and converts 10–15 per cent. of food energy into mechanical work and wastes the remainder in the form of heat. Sweat cools the body by evaporation; the latent heat of evaporation is the chief factor concerned.

It is a matter of common observation that illness due to exposure to heat, in the absence of sunlight, is common amongst workers in deep mines, and stokers in the stokehold of steamships. On the other hand, the blue-violet rays in sunshine have a noxious effect on patients suffering from pellagra or smallpox, and cause photophthalmia and some blindness. A certain amount can be learned from the effects of high environmental temperatures upon animals occupying different levels in the biological scale. Thus, frogs suffer from "heat-stroke" when the temperature of the water rises to 104° F.; it has been found that the lactic acid concentration in the blood and muscles of this amphibian rises to such a height that it becomes completely paralysed. Guinea-pigs begin to succumb to heat-stroke when the shade temperature rises to 110° F., rabbits when it reaches 116° F., and man at 130° F. In such circumstances the body is exposed to heat of such intensity that the natural powers of cooling are overwhelmed, the body temperature rises, increasing the respiratory and nitrogenous exchange, causing not only retention of heat but also overproduction.

Martin showed that the tropical sun can produce local heating of the skull to a depth of one to two centimetres of the skull surface, hair and tissues.

Acclimatization to hot conditions consists largely in training the sweat glands to function efficiently. Equally important is the redistribution of blood by the training of the circulatory system, whilst increase in plasma volume has also been shown to occur. The loss of solids in sweat causes cramps and loss of salts (Brunt).

An exceptionally exhaustive review of man's protection against the rays of the sun has been given by Critchly (1947). It is apparent that modern conceptions of the ill-effects of insolation have caused changes in former beliefs. The bogey of sun-stroke has, to a great extent, been laid. According to the review of the physiological effects of sunlight by Blum (1945), a white skin reflects 45 per cent. of sunlight as compared with 16 per cent. by a black skin. This means that, though the negro's integument is less sensitive to solar radiation, absorption of heat is greater. Wartime

experience has brought several changes into prominence. The over-clothing of the last century has now given way to a cult of nakedness and the vaunted health-giving effects of sun-tanned nudity are difficult to demonstrate, except that it definitely reduces the incidence of prickly heat, secondary skin infections and fungus disorders. The wearing of tinted glasses, especially of the polaroid variety, does protect the retina against tropical glare, whilst the artificial protection of the unshaded skin against the sun's rays shows that oils, fatty and greasy media do more harm than good for there is a tendency for the skin to become "fried." On the other hand preparations containing tannin are of greater service as a certain degree of keratinization is produced and benefit follows the use of pigmented washes containing flavine and permanganate of potash.

An immense amount of experimental work on the effects of heat upon human physiology has been carried out during the Second World War and since. So many papers have appeared on this subject and as many views have been expressed so that it has become very difficult to present a reasoned statement.

This rather extensive subject may be divided into the following headings: *Heat-hyperpyrexia and Heat-stroke*; *Heat-cramps*; Exercise-induced Heat Exhaustion; Water-deficiency Heat Exhaustion; Anhidrotic Heat Exhaustion; Sunburn; Chronic Heat Neurasthenia; Heat Edema.

Some of these terms may appear to be nebulous, but the Editor has done his best to make them intelligible.

HEAT-HYPERPYREXIA AND HEAT-STROKE

Synonyms.—Insolation; thermic fever; siriasis; sun-stroke.

These very striking effects of excessive heat are regarded as primary physiological phenomena and are attributable to impaired functioning of the heat regulating mechanism, peripheral or central. They are characterized by very high body temperature and profound clinical disturbances.

Geographical distribution.—Heat-hyperpyrexia appears to be remarkably restricted. Although this type has been reported in many countries, on careful investigation it will be found that a large proportion of the reputed cases are really other diseases, more especially cerebro-spinal fever, apoplexy, tuberculous meningitis, alcoholism, cerebral malaria, or some other phase of acute disease, but not true heat-hyperpyrexia.

The endemic areas are :—in America, the east coast littoral of the United States, more especially in the great towns, the Mississippi valley, the coast of the Gulf of Mexico, the valleys of the Amazon and of the La Plata, and the South Atlantic coast ; in Africa, the valley of the Nile, the coasts of the Red Sea, and a low-lying part of Algeria near Biskra ; in Asia, Syria, Iraq, the valleys of the Indus and Ganges, South Persia, Lower Burma, Tonquin, and South-East China ; in Australia, the Murray River district, the Queensland coast, and possibly the plains of Sydney. It is not met on the high seas, although it is well known on ships in the narrow, landlocked Red Sea and the Persian Gulf. During the 1914–18 war dangerous cases occurred most numerous in Iraq, especially during July, 1917, when for three days the temperature reached 122° F. in the shade, and 135° F. in the interior of double fly-tents.

Ætiology.—New-comers to the endemic areas and Europeans are more liable than natives or residents of long standing, and men over forty than those younger. All ages and both sexes are susceptible; but in consequence of their habits and more frequent exposure to the predisposing and immediate causes, men are more liable than women.

Heat-hyperpyrexia is generally attributed to direct action of atmospheric or solar heat on the body. Many theories of the *modus operandi* of this cause have been advanced. Among these may be mentioned superheating of the blood by the high temperature of the surrounding atmosphere. Hearne pointed out that heat-hyperpyrexia is associated with suppression of sweat, which may precede the onset of serious symptoms by 48 hours, for after prolonged exposure to high temperatures the sweat apparatus becomes exhausted and the glands cease to function. Recent investigations point to the importance of prickly heat (*miliaria*), and mammillaria in suppressing the functions of the skin. Coma, delirium and convulsions appear directly the body-temperature reaches 108°F. Hypodermic injections of atropine have been shown to predispose to heat-hyperpyrexia through action upon the sweat-glands. The cramps are attributed to coagulation of myosin in the affected muscles (Cajamian).

Blood chemistry.—Marked dehydration is associated with hæmoconcentration with an increase of hæmoglobin, sometimes to 110 per cent., and a corresponding increase in the red blood-cells. The leucocyte count is also slightly increased. There is a diminution of the blood chlorides and plasma bicarbonate, but a rise in lactic acid, blood-sugar and, usually, blood-urea (Marsh).

The earliest sign of hypochloræmia is low, or absent, urinary chlorides. The test is performed as follows:—To 10 drops of a 24-hour specimen of urine is added one drop of 20 per cent. potassium chromate solution; this gives a canary yellow colour. Silver nitrate (2·9 per cent. solution) is added, drop by drop, until the colour changes suddenly to brown. The number of drops of silver nitrate equals the amount of sodium chloride, in grammes per litre. Sugar and acetone are occasionally found in the urine, and also a trace of albumin and a few hyaline casts.

Pathology.—The cause of death is usually circulatory failure. A notable feature of fatal hyperpyrexia is the early appearance of rigor mortis. The blood is remarkably fluid, or but feebly clotted. The venous system is loaded, dark fluid blood pouring from the phenomenally engorged lungs and other viscera on section. Both blood and muscles are said to yield an acid reaction, more or less pronounced. The red blood-corpuscles are crenated and do not form rouleaux. If the post-mortem examination is made shortly after death and before decomposition changes have set in, the heart in early rigor mortis, particularly the left ventricle, will be found remarkably rigid; this is sometimes described as being of "wooden hardness." There may be some venous congestion of the meninges, and the brain shows small multiple hæmorrhages. On microscopic examination, necrotic changes in the ganglion cells, with chromatolysis of the nuclei, are found. The cerebro-spinal fluid is clear and under pressure. Cortical changes in the suprarenals have been described. In the lungs there is hæmorrhagic pulmonary oedema. The intestinal mucosa, as well as that of the stomach, is swollen, and exhibits patches of congestion. The temperature of the cadaver continues to rise after death, and may reach 114° F.

Among prodromata of a major attack, which may show themselves with greater or less distinctness for an hour or two, or even for a day or two, are great disinclination for exertion, pains in the limbs, drowsiness, vertigo, headache, mental confusion, sighing, anorexia, thirst, intolerance of light—sometimes accompanied by chromatic aberrations of vision—suffused eyes, nausea and perhaps vomiting, præcordial anxiety, suppression of sweat, urinary irritability, sometimes a sense of impending calamity, an hysterical tendency to weep, and a quickened pulse.

Acute heat-stroke.—The first indication of anything seriously wrong may be a short stage of restlessness, or possibly of wild delirium. This brief preliminary stage rapidly culminates in coma and high fever, quickly passing into hyperpyrexia which may reach 112° F. The pupils are contracted, except immediately before death when, along with the other sphincters, they relax. The face is congested and the muscles rigid. The reflexes are partially or wholly in abeyance. There may also be, especially in the graver cases, free watery purging, the dejecta as well as the skin of the patient emitting a peculiar and distinctive mousy odour. The scanty urine may contain indican, blood-corpuscles, albumin and casts. The cerebro-spinal fluid is normal in appearance and its pressure slightly raised.

Unless active measures to lower temperature are taken early and vigorously carried out, in the great majority of instances, death will occur within a few hours, or even minutes, of the onset of insensibility. The immediate cause of death is generally the failure of respiration. Rarely do cases linger for a day or two. Partial recovery is sometimes followed by relapse. In favourable cases the disease usually terminates by crisis. Convalescence is rapid. Unless the patient is moved into different surroundings a relapse may occur; two or even three have been recorded.

The death-rate may be materially reduced by early and judicious treatment. In Iraq, during the 1914–18 war, the case-mortality among British troops was about 8 per cent.

Diagnosis.—The high fever is sufficient to differentiate heat-hyperpyrexia from sudden insensibility caused by uræmia, by diabetic coma, by alcoholic and opium poisoning, and by all similar toxic conditions. Carbon monoxide and hydrogen sulphide poisoning must also be thought of. Cerebral hæmorrhage, particularly pontine, may, after some hours, be followed by high temperature; but here the febrile condition follows the insensibility, whereas in heat-stroke the febrile condition precedes insensibility. Diagnosis from a cerebral malarial attack may be very difficult; chief reliance has to be placed on the history, if obtainable, on the condition of the spleen, and especially on the result of microscopic examination of the blood; but sometimes the subtertian parasites may not be demonstrable for two or even four days from the onset. Malarial fevers and the early stages of the eruptive fevers in children are very apt to be regarded as heat-stroke, particularly if there has been recent exposure to a hot sun. Cerebro-spinal fever, so often mistaken for heat-hyperpyrexia, may be recognized by the occipital retraction, the irregular pupils, the frequent occurrence of strabismus, Kernig's sign, the comparatively low

and fluctuating temperature, the associated herpes, the initial rigor, and its duration. Lumbar puncture will, of course, give a clear differentiation. The fluid is often under high pressure, but is clear in heat-hyperpyrexia, and lumbar puncture should be performed in these cases, not only for diagnosis, but as a therapeutic measure. Uncomplicated heat-stroke is accompanied by hypochloræmia, dehydration, absence of urinary chlorides, excess of lactic acid, and low content of bicarbonates in the blood.

Marsh states that during a heat-wave in the Persian Gulf mild cases of heat-exhaustion are usually in the majority, and so it is difficult, sometimes, to distinguish cases of pure fright from genuine cases. Real cramps constitute a valuable diagnostic sign. They are so extremely painful that the patient cannot sustain a conversation and the affected muscles can be felt to contract forcibly.

Men of fifty years of age or over, or young men who have been suddenly introduced to a hot climate, should be carefully examined, for they may develop rapid hyperpyrexia without any of the usual premonitory signs. The correlation of heat deaths with increasing age is probably due to progressive diminution in the heart reserve.

Treatment.—Treatment must be instituted at the earliest possible moment. A few hours' delay may mean death to the patient. In all fulminating fevers, including heat-hyperpyrexia, in warm climates, if malaria be suspected, particularly if the subtertian parasite be discovered in the blood, quinine should be injected intravenously or intramuscularly at once (7–10 gr. of the dihydrochloride); this dose should be repeated three or four times at intervals of four hours. Should there be any suspicion of alcoholic poisoning, the stomach should be washed out. In every case of heat-stroke, whether it has been deemed advisable to administer quinine and other antimalaria drugs, or not, attempts must at once be made to reduce temperature by such rapidly acting measures as the cold bath, or ice applied in various ways to the head and body. The patient should be placed on a wet sheet supported upon bed cradles, thus forming a moist chamber in which he lies; the whole may rest upon a rush-covered bed or "angareeb." Fanning with wet Turkish towels is recommended. Mackintosh sheets must be avoided. The continuous water-spray with iced water, together with an electric fan, simulates the natural process of sweating to the best advantage. In the absence of electric fans, an iced wet sheet may be wafted up and down over the patient's abdomen by a punkah-like arrangement. Rubbing the skin with ice, by constricting the capillaries, apparently only obstructs evaporation. A thermometer should be kept in the rectum and the application of cold should be discontinued as soon as the thermometer in the rectum has sunk from 106° to 102° F., or from 109° to 104° F. If powerful antipyretic measures are carried beyond this point the fall of temperature may continue below the normal, even as low as 91° F., and dangerous collapse ensue.

Fluid must be given in large quantities, as 0.25 per cent. saline drinks or, if the patient cannot swallow, as intravenous normal saline, of which quantities up to 20 pints may be given. The fluid and salt requirements are regulated by the appearances of dehydration, the blood concentration

(estimated by red cell count and percentage of hæmoglobin), the amount of urine and the blood pressure. Intravenous saline is indicated if the systolic blood pressure is below 100. It must be given with great care, for the cardio-vascular system may be unable to deal with it. If the blood pressure does not rise, the patient may die of pulmonary oedema, which may occur after 9 pints has been administered.

On discontinuance of the iced sheet, the patient should be wrapped in a dry blanket; very likely, perspiration, a favourable sign, will then set in. Stimulants may now be necessary. Strychnine, owing to the marked tendency to convulsions in heat-stroke, must on no account be used as a cardiac stimulant; Chandler, as the result of his large experience, recommended the injection of 40 min. of tincture of digitalis. Convulsions are best controlled by cautious venesection. As death in heat-stroke generally results from failure of respiration, Hearne and others strongly recommended artificial respiration when the breathing threatens to become suspended; it should be maintained for half an hour or longer. Lumbar puncture is indicated as a rational method of relieving intracranial pressure. Gastric cases should receive a liberal supply of bicarbonate of soda—30 gr. every two hours. Diarrhoeic and dysenteric cases are specially liable to hyperpyrexia because of loss of fluid. Nourishment is needed; sweetened diluted tinned milk may be used.

During convalescence great care must be exercised to shield the patient from all influences calculated to provoke relapse. The power of sweating may be in abeyance for three weeks or longer.

Sequelæ.—In some (McAlpine, 1946), mental confusion with incontinence, aphasia, pyramidal and cerebellar signs persist. As recovery proceeds the patient becomes more orientated, ceases to confabulate, and shows prognostic improvement in memory similar to that after a head injury, but in a small percentage a gross memory defect for recent and past events persists, accompanied by lack of interest, childish behaviour and incontinence. Inability to talk may be due to aphasia or gross dysarthria. Signs of unilateral or bilateral hemiplegia clear up, but the most constant sequel is a cerebellar picture which manifests itself in ataxia and rarely in nystagmus. Sometimes the picture of disseminated sclerosis is reproduced.

Prophylaxis.—Patients in hospital are especially liable to heat-hyperpyrexia. The most valuable practical method is to attempt to forestall it by periodically inspecting the patients to find out those with commencing suppression of sweat, urinary irritability, restlessness and insomnia.

A heat-stroke hut, or treatment room, or even a heat-stroke ward, are most desirable additions to hospital equipment in the tropics.

An improvised cooling apparatus can be made by filling the radiator of a lorry with ice and driving the fan-driven air by means of a tunnel into a one-bedded bunk (Morton).

A special refrigerating apparatus consists of a horizontally placed ammonia compressor working in conjunction with a brine-circulating system. At Masjid-i-Suleiman in South Persia (Anglo-Iranian Oil Fields)

heat-stroke cases and, indeed, all cases of fever, are kept in outlying stations during the heat of the day until the cool hours between midnight and five a.m., in a cold-storage chamber attached to the ice-plant. During the coolest part of the night they are put into a fast ambulance and taken to the nearest heat-stroke hut where they are kept until complete recovery has taken place. Such accommodation should be provided for 10 per cent. of the population exposed to risk, in order to provide for the rush of cases during a heat wave.

Buildings must be so constructed that they do not retain heat, and cool down quickly. The roof should be double, enclosing a wide air space, or it should be of thick thatch, projecting well and shading the upper walls. A ventilated verandah should extend all round, supporting hanging curtains of strong canvas, surfaced on both sides with aluminium foil. Double walls should be provided.

Efficient methods of cooling the air are employed in industry in many parts of the world. These include methyl chloride, or ammonia refrigerating machines, or the cooling powers of evaporating water at atmospheric temperatures and in *vacuo*. Air-conditioning of houses and dwelling-rooms is commonly found in New York and other American cities, and the matter is solely one of expense.

The cost of maintaining a cool chamber is £400-£500 per annum.

The drink available for all workers in endemic areas of heat-stroke should consist of: sodium chloride 6 oz., potassium chloride 4 oz., water 1½ pints. Of this concentrated solution, 17 fluid ounces are added to 3 gallons of water for drinking; a flavouring may be added (Dunlop, McNee and Davidson).

As the result of these measures heat-stroke has been greatly reduced and has almost ceased to count as a cause of invalidism.

HEAT-EXHAUSTION

The condition known as heat exhaustion can be induced by exercise, salt loss, water-deficiency, or depression of sweating. The symptoms and signs are similar to those experienced in ordinary environment, but relatively more severe. Exertion is usually relaxed at the state of exhaustion, but actual collapse may ensue and this may take the form of syncope on standing erect. A similar clinical state can be attributed to inadequate replacement of salt loss which may become chronic with general asthenic symptoms, vomiting and sometimes cramps. The urine is very scanty, concentrated and free from chlorides. There is hæmoglobin concentration and raised plasma proteins. It may be fatal, but may be relieved by restoration of blood chlorides. Ladell, who at one time taught that salt deficiency was the major factor, now thinks that water debt—in those who drink too little, is the predisposing cause. The loss of much extra-cellular water makes a person susceptible to heat exhaustion, while depletion of intracellular water may be dangerous. The data have been obtained on soldiers serving in Iraq as well as in hospital patients. All men lose weight in hot weather, and the greatest loss takes place in those with the highest chloride sweat concentration.

Another form of heat exhaustion is attributable to lack of drinking

sufficient water in a hot environment and is characterized in its early stages by weariness, sleepiness and dizziness. Dyspnoea and cyanosis soon develop so that a walking pace cannot be maintained and a stage of exhaustion is reached. There are very few grounds on which to separate the condition described as *Thermogenic anhidrosis* (or Type II of Ladell) which is encountered only in the second half of the summer. It is a fatigue phenomenon. There is usually dizziness, dyspnoea and anorexia. Frequency of micturition often heralds the cessation of sweating and is accompanied by *prickly heat*. Vomiting, cramps and cardiovascular signs are absent. The clinical picture suggests a breakdown of the defence mechanism of the body against heat. The urine volume is large, of a low specific gravity, normal salt concentration and low urea content. The incidence of this type can be reduced by a break of a few days in a cool climate. Whatever the physiological principles in the production of heat exhaustion there is no doubt that involvement of the skin plays a dominant part. *Mammillaria* is a skin condition associated with anhidrotic heat exhaustion. The appearances are quite distinct from those of prickly heat. The affected skin is studded with pale, firm elevations which are roughly circular and about 1 mm. in diameter and they bear no constant relation to the hair follicles or openings of sweat ducts. Their colour is due to less contained blood and less melanin than the surrounding skin which feels rough like a nutmeg grater. The eruption is uniformly distributed from the neck over the trunk as far down as the waist and lateral aspects of the upper arms. After exposure to heat the lesions become more prominent. *Mammillaria* may last four months. In humid climates, *mammillaria* invariably follows prickly heat, also the rule does not hold so much in dry climates.

It is possible to restore sweating of a dry area of *mammillaria* by the application of anhydrous lanoline which is known as the "lipoid response." The principle is that application of fat to the skin prevents the evaporation of sweat. Prickly heat (see p. 654), known also as *Miliaria rubra*, is attributable to extensive sweating, particularly in humid environments and is accompanied by intense prickly sensations.

SUNBURN

Is an acute erythema which is not unknown in sunbathers even in temperate climates. In its exaggerated state in the tropics it is followed by vesiculation and extensive desquamation of the skin. If extensive, it may cause malaise, headache, fever and sometimes vomiting. In hot climates it may interfere with heat regulation since the affected areas lose vasomotor control and do not sweat. Sunburn is followed by the familiar brown pigmentation.

HEAT NEURASTHENIA

This is by no means an uncommon state in any hot country, and also in badly ventilated workshop or factory. The patients complain of ill-defined symptoms of fatigue, extreme tiredness, irritability and inefficiency. Acute and chronic stages are recognized. The latter may simulate the "effort syndrome" with difficulty in concentration, "blackouts," loss of weight and appetite.

HEAT OEDEMA

This is very common in Europeans, especially in young women on their first contact with true tropical heat. To ships' captains it is familiar as the "Columbo flop." It is characterized by oedema of the extremities, especially the ankles. It ranges from a feeling of tightness of footwear to an incapacitating swelling of ankles and lower legs. The swellings are usually transient and clear up on acclimatization and on return to temperate conditions.

HEAT CRAMPS (MINER'S CRAMP; STOKER'S CRAMP)

Heat cramps frequently accompany heat exhaustion and consequently are commonly found in hot countries. They are attributable to salt deficiency. They come on suddenly and are brought on by activity and exercise and there is always a reduction in the chloride content of the blood plasma. They may be accompanied by other evidences of hypochloræmia. When they are produced by exertion, muscle action currents show definite changes and may be excited by faradic stimulation. Two main factors appear to be involved—intracellular over-hydration and chloride loss. These cramps are immediately relieved by the administration of salt.

Acclimatization.—Some organizations in the tropics endeavour to avoid the ill-effects of heat by ensuring fitness and acclimatization of the workers. In the Witwatersrand gold mines, candidates for employment are subjected to an *exercise tolerance* test in rooms artificially heated to 94° F., wet-bulb, and are then graded on their reactions, suitable candidates being put through a further course involving exposure to high temperatures in stages and lasting, sometimes, for fourteen days. Soldiers should be given lectures on the precautions necessary in hot climates.

Fewer casualties occur from heat among men born and bred in hot climates than among those reared in temperate climates. While there is a general agreement that excessive alcohol consumption is contra-indicated, less attention has been paid to the profound effects that may arise from shortage of water and to the importance of replacing salt lost in sweat. The minimum daily fluid requirement in the hot season is 16 pints, and a man doing hard manual work may take 4 gallons. A daily ration of $\frac{3}{4}$ oz. of salt is essential, and should be taken for several days before entering a heat stroke area, and continued throughout residence there. There is no evidence that alcohol in moderation is harmful. Constipation in the hot season is almost physiological and must be avoided, but care should be taken that when saline purges are given, plenty of fluid is drunk, since a watery motion may induce dehydration, and a patient may be constipated because he is already somewhat dehydrated.

In the 1939-45 war it has been noted that, during the hot weather of 1942, nearly three-quarters of the cases of general effects of heat amongst troops in Persia and Iraq occurred before, during and after disembarkation. Many could have been prevented, had adequate precautions been taken on board ship. High atmospheric humidity with a wet bulb temperature of 80° F. is the danger point.

It is dangerous for persons who have suffered from heat-hyperpyrexia to return to the conditions or surroundings that brought it on in the first place.

Section II.—VITAMIN DEFICIENCY DISEASES (AVITAMINOSES)

CHAPTER XXVI

BERIBERI AND OTHER VITAMIN B₁ DEFICIENCIES

Synonyms.—Kakke ; Barbiere ; Polyneuritis Endemica.

Definition.—Beriberi is a form of multiple peripheral neuritis occurring endemically, or as an epidemic, in most tropical and sub-tropical climates, and also, under certain conditions, in more temperate latitudes. The mortality may be considerable, usually from cardiac failure.

Geographical distribution.—Until recently extensive, corresponding with tropical and subtropical belts. Formerly the scourge of mines and plantations of Malaya, China and Indonesia; amongst coolie gangs on engineering works such as Panama Canal and Congo Railways; in Dutch army in Sumatra and in Japanese navy. It is still fairly common in ports and cities of Japan, in China, Philippines, India and Africa.

Epidemics have been reported in W. Australian aborigines and amongst Chinese in E. Australia.

Beriberi was once seen in a lunatic asylum in Dublin, as well as in institutions in U.S.A. and France; also in fishermen in Newfoundland and N. American coast, in Westman Islands, Iceland (1938), living on fish diet deficient in vitamin B₁.

Epidemiology and endemiology.—*Sex, age, occupation.*—Beriberi attacks both sexes. It is not uncommon in the breast-fed infants of beriberic mothers. This form, called *infantile beriberi*, may declare itself in varying ways.

Ship beriberi.—Beriberi was prevalent among the native crews, more rarely, though occasionally, among the European officers and sailors, of ships on the high seas.

From 1894 up to 1920, or thereabouts, the disease was common in European crews of Swedish and Norwegian ships, which were in far better sanitary condition than British ships, and yet beriberi was comparatively rare in the latter. The modern explanation is that, since the year named, the crews of the Norwegian mercantile marine have been provided, under the terms of a statute, with bread baked from white flour, or a mixture of wheat and rye, so that their diet was inadequate in vitamins.

If a fowl or pigeon be fed exclusively on "*paddi*," that is, rice from which the husk has not been removed, it will thrive and very likely gain weight; but if it be fed exclusively on a diet of white rice and grain, that is, rice from which the pericarp has been completely removed, after a short time, it will show signs of peripheral neuritis, lose weight and, if the exclusive diet be persisted in, die with all the signs of a multiple peripheral neuritis. This *polyneuritis gallinarum* (or *p. columbarum*)—as it is called—is evidently the result of the deprivation of some element of food essential for the proper nutrition of the nervous system of the bird, and the element is located in the pericarp and germ of the rice grain (Figs. 64, 65). Almost miraculous recoveries in the stricken birds take place after hypodermic injection of an extract of the germ centre of wheat or other cereal.

The greater part of the rice grain is starch, and covering the central starch

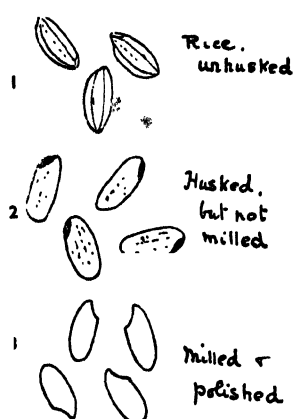


Fig. 64.—Showing the various stages in milling the rice grain. 1, Rice grain in the natural condition enclosed in the husk or enclosing glumes; 2, After removal of the husk, but retaining the pericarp or “silver-skin” and the embryo; 3, After milling and polishing; both “silver-skin” and embryo are removed and the grains are “polished” by rubbing with talc between sheepskins. (After Chick and Hume, “*Trans. Soc. Trop. Med. and Hyg.*”)

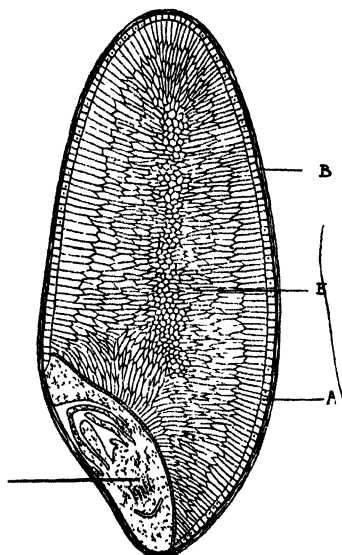


Fig. 65.—Diagram of longitudinal section through a grain of wheat showing (a) aleurone layer of cells forming the outermost layer of the endosperm, removed with the pericarp during milling; (b) pericarp forming the branny envelope; (c) parenchymatous cells of the endosperm; (g) embryo or germ. (By permission of H.M. Stationery Office, from Dr. J. M. Hamill's “*Report on the Value of Bread made from Different Varieties of Wheat.*”)

core there is a thin aleurone layer containing the proteid and fat constituents of the grain. Externally there is an adherent layer, the pericarp, which varies in colour from red to white according to the variety of the rice. The pericarp contains the salts. The grain itself is covered by a husk, which is discarded as chaff.

Fraser and Stanton showed—and their observations have been abundantly confirmed—that the antineuritic element is located in the pericarp of the rice grain, in the aleurone layer, and in the embryo of the grain, that it is soluble in water and alcohol, is stable in acid but unstable in alkaline solutions, is thermolabile—being destroyed by a temperature of 130° C.—and that it is dialysable; that is not a phytin or a fat, although itself not containing phosphorus.

The polyneuritis of the fowl is identical clinically and aetiological with the polyneuritis, called beriberi, occurring in man. For, as has been both accidentally and intentionally done, if the same experiment with rice-feeding be tried on man the result is identical—beriberi is induced. Thus, following the lines of the earlier experiments of Fletcher, Fraser and Stanton, Strong and Crowell conducted a series of experiments on twenty-four life-sentenced prisoners, and were able to prove (a) the non-communicability of the disease, and (b) its production in man solely by means of diet. A similar condition has been produced in rats.

Acting on these findings, the governments of Singapore and the Federated Malay States forbade the use of white or polished rice in their jails, lunatic asylums, schools and hospitals, with the result that beriberi, which until then had been the cause of an enormous mortality and morbidity, has been practically banished. Corresponding results have accrued from the same practice in Indonesia, the Philippines, and elsewhere. In India decorticated rice is practically the staple diet of many millions, though beriberi is endemic only in a few circumscribed areas in Bengal and Assam, the north-east coast of Madras, the coast of Burma, and certain river valleys. The basal factor in India must be a fundamentally poor diet, whether of rice or other food grains. The period of development of beriberi in man was determined by Fraser and Stanton as between eighty and ninety days.

Vitamin B₁ (aneurin: thiamin).—Vitamin B₁ is composed of pyrimidine and thiazole nuclei. It is 2-methyl-5-(4-methyl-5- β -hydroxyethyl-thiazolium chloride) methyl-6-amino-pyrimidine hydrochloride (C₁₂H₁₇ON₃S), a colourless water-soluble crystalline substance containing a molecule of water of crystallization and melting at 248–250° C. In dry conditions it is stable at 100° C. for twenty-four hours. The rate of destruction is increased by presence of water and alkali. It is oxidized to thiochrome by potassium ferricyanide in the presence of alkali.

Destruction in ordinary cooking processes is not very great, if soda be not added to vegetables. Pressure cooking, even when rapid, causes considerable destruction. The destructive action of sulphites is of some importance, since these are used in the preservation of fruit pulp and juices, and depends on the pH of the medium. Vitamin B₁ is destroyed on autoclaving and largely inactivated when yeast and liver are subjected to heat under pressure. When subject to mild oxidation with potassium ferricyanide, the alkaline solution is converted to *thiochrome* which exhibits intense blue fluorescence under ultra-violet light, a reaction employed in the estimation of B₁. Thiochrome is devoid of any vitamin-like action.

B₁ is widely distributed in raw foodstuffs, the richest sources being whole cereals, especially the pericarp and germ (*see* p. 389), yeast, pork and pulses. Vegetables, including potatoes, are an important source. The diet of the working classes in Britain is so deficient in B₁ that even now white could with advantage be replaced by wholemeal bread. Yeast is an exceptionally potent source and should be used as a dietary supplement when large quantities are required. Milk is a poor source.

The larger part of B₁ is stored in the liver, kidneys and muscles, and it is abundant in the normal heart. Depletion occurs most rapidly in the muscles and is slowest in the brain. B₁ is excreted in the urine, and the kidney concentrates it from the plasma to a marked degree, perhaps twenty times or more, but it appears that only a small proportion of the vitamin given by the mouth, or by injection, is excreted in the urine, the rest being destroyed in the body. It is also excreted in the milk but no appreciable quantity in the faeces. Harris and Leong (1936) believed that excretion of less than 12 I.U. per day in the urine is evidence of B₁ deficiency.

Human requirements.—An increase in metabolic rate increases B₁ requirements. Thus, beriberi is more prevalent amongst stokers than sailors, owing to their greater physical exertions. Similarly, males suffer more from beriberi than non-pregnant women, due to harder physical work. In Manila there is a high incidence of beriberi among pregnant and nursing mothers. As the metabolic rate rises during fever there is apt to be an association of beriberi with malaria and other pyrexias.

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The International Unit is the antineuritic activity of 3 γ of pure B₁ (i.e. 333 I.U. = 1 mgm.). The minimum daily B₁ requirement in international units is expressed in Cowgill's formula: daily calorie intake $0.0284 \times \text{weight in kilos} \times 0.05$. Therefore, for an adult of 70 kg. (11 st.) on 3,000 calories a day the minimum requirement would be approximately 300 I.U. or 1 mgm. The figure is the physiological minimum, but 500–700 I.U. (1.75 mgm.) is the desirable intake. The metabolic rates in pregnancy, lactation, infancy and childhood, per unit of body surface, are greater than in normal adult life; therefore a greater B₁ requirement is necessary. Infants require approximately 50–60 I.U. (0.2 mgm.). Up to adolescence the B₁ requirements increase with age. In hyperthyroidism and during exercise the B₁ requirements are increased.

The significance of B₁ is in relation to carbohydrate metabolism, rather than to its direct effect on the nervous system. Human and avian nervous systems can be deprived of B₁ with impunity when no carbohydrates are given. B₁ acts as a catalyst in carbohydrate metabolism of the nerve cell and heart muscle. In the absence of B₁, cellular carbohydrate metabolism breaks down at the stage of pyruvic-acid formation. This substance accumulates in the cells, where its presence can be detected. It is, however, an error to suppose that pyruvic acid is toxic. The mechanism by which this is effected is known as the *citric acid cycle* of Krebs. This cycle consists essentially of the formation of citric from pyruvic acids, followed by a stepwise degradation of citric acid. The reactions are catalyzed by enzymes. Peters and his colleagues believe that B₁ functions as a co-enzyme in the metabolism of carbohydrates and plays a part in the oxidation breakdown of pyruvic acid. Therefore accumulation of this acid or of pyruvates in the blood and central nervous system, and its excess in the urine, is related to the deficiency of B₁. It is therefore essential for normal growth and the maintenance of body weight.

INCIDENCE.—The incidence of beriberi is greatest in those regions where polished rice and refined cereals form the bulk of the diet. It constituted one of the most potent causes of mortality in Japanese infants. From 1920–1929 there was an average of 17,000 deaths from this cause in Japan.

In people living on an inadequate diet the raised basal metabolic rate resulting from fever increases the liability to beriberi—as after smallpox, cholera or meningitis. In China, for instance, 10 per cent. of patients show some reflex abnormality suggesting latent beriberi. Thus, any lowering of the general resistance leads to the development of polyneuritis. Breast-fed babies born of mothers suffering from the disease are themselves liable to it.

Pathology.—The post-mortem appearances of beriberi resemble the accepted descriptions of peripheral neuritis. There is a degeneration of the peripheral nerves—more especially of their distal ends—and there is secondary atrophic degeneration of muscle, including that of the heart. Degenerative nerve-changes may be detected in the nerve-centres and throughout the implicated neurones, as in other forms of peripheral neuritis. There is invariably an involvement of the vagus with degenerative changes in its root in the floor of the fourth ventricle. Microscopically, the nerve-trunks show changes, from a slight medullary degeneration to complete destruction of the nerve (Wallerian degeneration). Regenerative processes occur side by side with the degenerative (Fig. 66). As a rule, some fibres in the vagus and sympathetic escape; thus, the cardiac branches in the heart-muscle and the bronchial and oesophageal twigs are usually unaffected. According to Vedder, the membranes of the spinal cord are often congested and oedematous; scattered fibres in all tracts show the same kind of changes as the peripheral nerves. Degenerative changes are also found in the anterior and posterior horn cells, as well as in the sympathetic ganglia. If there is anything peculiar about the post-mortem appearances in beriberi, it arises

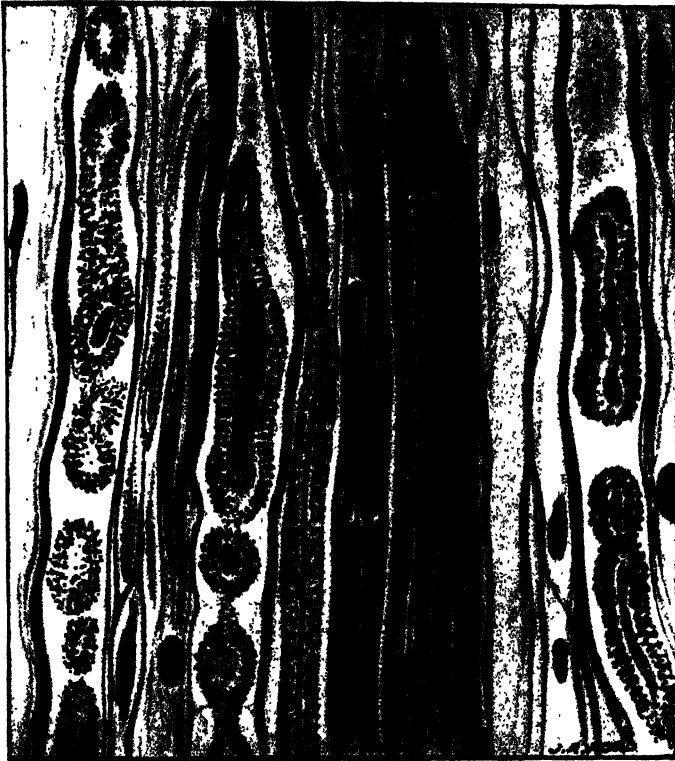


Fig. 66.—Longitudinal section of external popliteal nerve in beriberi.

One myelinated fibre in centre is practically intact; the others show typical fragmentation of myelin sheath with swelling of remains of nerve-fibre.

(From a preparation by Dr. A. C. Stevenson.)

from the somewhat special implication of the central and peripheral organs of the circulation—namely, dilatation of the heart, especially of the right side, and great accumulation of blood in the right heart and in the veins. In addition, there is a marked liability in many cases to serous effusion into the pericardium, pleural cavities, peritoneum, and cellular tissue. This very marked liability to serous effusion and the tendency to cardiac dilatation may be said to be more or less distinctive of beriberi as compared with other forms of multiple neuritis. Oedema of the cardiac muscle naturally interferes with the normal fluid exchange within the fibres and therefore with its contractibility. According to Mebius, when vitamin B₁ is deficient, full muscular contractibility is impossible owing to water absorption (hydropic degeneration of Wenckebach). The average weight of the Japanese heart in beriberi is 368 grm. (normal 300 grm.). The enlargement is particularly noticeable on the right side, especially the right auricle, and the walls are paper-thin. Without doubt, water-retention in beriberi is of the greatest importance in elucidating the mechanism of symptom production. Oedema of the lungs also is not uncommon, and has, probably, a pathology similar to that of the connective-tissue oedema. There is no nephritis, but pressure congestion of the liver (nutmeg liver). Duodenitis is frequent.

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The general affection of the whole nervous system, involving the central and peripheral structures, is identical with that found in diphtheritic or alcoholic neuritis.

Symptoms. *Primary Beriberi (Naturally-occurring disease).*—Beriberi assumes varying clinical forms according to the extent and position of the nervous lesions. It is insidious in onset, but it may occasionally be ushered in by acute symptoms ending fatally within a few hours without



Fig. 67.—Ataxic or paralytic beriberi, showing characteristic attitude.

development of any symptoms referable to the nervous system. As a general rule, it is classified into two main forms, according as the peripheral nerves or the cardiovascular system are most affected. The former is known as paralytic or "dry" beriberi, the latter as cedematous or "wet" beriberi. It must be understood that in all its forms beriberi is the same disease, and that a clinical classification has but a conventional value. Sudden death from heart failure may ensue, especially in cedematous cases.

Paralytic beriberi (Fig. 67).—There is a certain amount of anæsthesia or numbness of the skin, particularly over the front of the tibiae, the dorsa of the feet, the sides of the thighs, perhaps also of the finger-tips, and one or two areas on the arms and the trunk. Deep sensibility (Abadie's sign), elicited by compression of the Achilles tendon, is usually numbed or

entirely lost. The calves may be strikingly thin, the gastrocnemii flabby, and if they and the neighbouring muscles are handled somewhat roughly, particularly if they are squeezed against the underlying bones, the patient will call out in pain and try to drag the limb away. Toe and foot-drop can frequently be demonstrated. Weakness spreads upwards, first involving the extensor muscles of the leg, and then the extensors and flexors of the thigh. The skin of the limbs becomes shiny. The thenar, hypothenar, plantar and arm muscles, like the calf muscles, may be wasted, flabby and exhibit fibrillary twitchings. Very probably there is a loss of fat, the

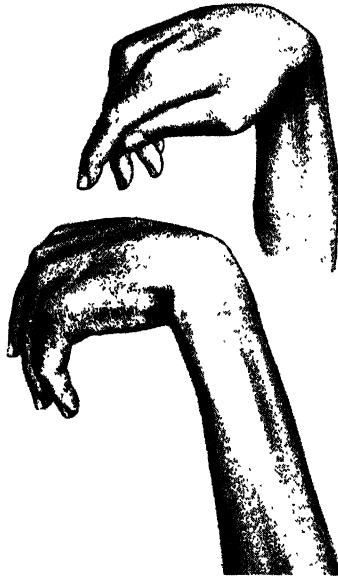


Fig. 68.—Paraplegic beriberi, showing wasting of extensor muscles and wrist-drop.

panniculus adiposus being everywhere meagre. If tested electrically, the muscles exhibit the reaction of degeneration. If the knee reflex be tested in the usual way, it is at first increased, but after the first week there will be no response whatever; nor can any clonus be elicited, but occasionally a reflex contraction of the hamstrings may take place, giving a false impression of a knee-jerk. As a rule, all the deep reflexes are lost; but the superficial, unless in extreme paresis and muscular atrophy, are usually present and more or less active. If, in severe cases, the patient is set to button his jacket or to pick up a pin, possibly he has a difficulty about it, or perhaps he cannot; he may bungle and fumble like the advanced ataxic. The fibres of the affected muscles, when struck with a patellar hammer, often contract locally in a particularly painful manner known as myœdema. There may be wrist-drop (Fig. 68).

There is more than ataxia, however, for the hand-grasp is so enfeebled that the patient may have a difficulty in holding his rice-bowl as well as in feeding himself. There is no tremor of the hands; and never, or very rarely, is there any paresis of the ocular muscles, or of the muscles of the face, of mastication, of the tongue, or of the pharynx. The sphincters and bladder operate satisfactorily, and the functions of the alimentary canal are carried on fairly well, although there is often some dyspeptic distension and oppression after food. If the patient can walk at all, his gait will be markedly ataxic; but, in addition to want of co-ordinating power, there is great muscular weakness. If he is laid on the bed and asked to raise his legs, he is perhaps hardly able to get them off the mat, to cross them or to place one foot on top of the other. Very probably he is the subject



Fig. 69.—Wet or edematous cardiac beriberi. (Philip Manson-Bahr.)

of marked foot-drop, so that he drags his toes when he attempts, in walking, to advance the foot; he has therefore to raise the foot very high, letting it fall on the ground with a flop when he brings it down again (steppage gait). His ataxia and his muscular weakness, as well as the partial anæsthesia from which he suffers, force him to adopt a variety of devices to assist him in progression. Although mental symptoms are uncommon, defects of memory often occur.

The general health is good, for the most part; the tongue is clean, the bowels are fairly regular, there is no fever. Loss of sphincteric control does not occur until very late. Digestion, assimilation, and excretion are satisfactory.

Cardiac beriberi, wet beriberi.—Instead of being wasted, as in paraplegic cases, the face is puffy and heavy; the lips possibly slightly cyanosed; and the arms, hands, trunk, legs, and feet are distended with edema (Fig. 69).

It may be thought at first from the œdema that it is a case of acute nephritis, but an examination of the scanty, dark-coloured urine shows that it is of high specific gravity and contains no albumin, or only a mere trace. Careful observation will discover that the œdema is somewhat firmer than that of nephritis and, in not a few instances, that it does not involve the scrotum. Occasionally it is peculiarly localized and fugitive. A bruit and other evidences of dilatation of the heart are discovered. Occasionally irregularity may be associated with slowing of the heart-beat, and heart-block may occur in such cases. The liver is frequently swollen and tender. The lungs may (or may not) present signs of single or double hydrothorax, but they themselves are healthy. The patient can hardly walk—partly from breathlessness, partly on account of mechanical interference by the dropsy with the movements of the legs—partly, perhaps, from some degree of paresis. He may have ankle-drop; if firm pressure be brought to bear on the calf-muscles through the œdema, signs of hyperæsthesia of the muscles may or may not be elicited. Knee-jerks are generally absent, and there is numbness of the shins and finger-tips. The tongue is clean, the appetite fair, and there is no fever. But there may be præcordial distress and even pain, and, as this is aggravated by a full meal, the patient eats sparingly. The amount of urine is generally very much reduced—even to a few ounces.

In this patient, therefore, there are the same signs of peripheral neuritis and of dilatation of the heart as in the other cases. In addition, there is a somewhat firm œdema, which is not altogether cardiac, but, as its character and the circumstances in which it is found suggest, is probably connected with the play of transudation and absorption in the connective tissues.

When the heart is examined, if the case be at all recent or moderately severe, the impulse is diffuse; there is epigastric pulsation; the carotids throb violently; and there is that peculiar wobbling, pulsating movement in the jugulars that denotes tricuspid insufficiency. "Pistol shot" sounds are heard on auscultation over the larger arteries. On percussion the præcordial area is frequently enlarged, perhaps very greatly so, especially to the right; and on auscultation loud bruits, usually systolic in rhythm, may be heard. Marked reduplication of the sounds, particularly of the second, is noted. The auscultator may be impressed, in a large proportion of cases, by the peculiar spacing of the intervals between the sounds. It may be hardly possible to tell by the ear alone which is the first pause and which is the second. They seem alike in point of duration (tic-tac rhythm); so that the sounds resemble the beats of a well-hung pendulum clock, evenly spaced, and not, as they are in health, separated by a long and a short interval. It will also be observed that the heart is very irritable, easily quickened by exertion. In addition to peripheral neuritis, there is serious disease in the circulatory system, particularly in its innervation; there is dilatation of the right side of the heart, and a state of relaxed arterial tension. Paralysis of the left recurrent laryngeal nerve by a grossly distended right auricle has been recorded. There is a wide range in the pulse-pressure, and Aalsmeer and Richter have shown that there is almost invariably a low diastolic blood-pressure which can be influenced by the injection of adrenaline (the adrenaline effect). Pitressin

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raises the diastolic pressure from almost zero to 75 mm. and the venous pressure falls ; this beneficial effect may last 1½ hours.

Usually, in well marked cases, the electrocardiogram shows distinct changes of low voltage and an indefinite inverted or flattened T wave in I, II and III leads, shrinking of the P—R interval and prolongation of the Q—T interval.

The cardiac enlargement in human beriberi was ascribed by Aalsmeer and Wenckebach to oedema of the heart-muscle, which results in an interference with its contractile power without disturbance of its excitability.

Wenckebach investigated a number of cases of cardiac beriberi in Indonesia and Singapore, taking special precautions to inject hardening fluid, and he was thereby able to confirm the presence of certain gross anatomical changes which are demonstrable during life by radiography. The whole of the right side of the heart is enlarged, while the left remains comparatively small ; the conus arteriosus takes part in the change. The large systemic veins are commonly dilated, and as much as three litres of blood may escape from the right auricle. The extrapericardial pulmonary vessels are not abnormally congested. Microscopic examination of the heart muscle after death reveals intracellular oedema, sarcolysis, and hydropic degeneration, probably primarily due to excess of lactic acid, brought about by defective oxygenation. The primary lesion is, therefore, a loss of contractibility of the heart muscle, related to water retention, with consequent loss of peripheral vascular tone. The clinical picture and its response to adrenalin and pitressin, together with the lowering of diastolic pressure, accord with these findings.

Aalsmeer employed the results of these observations as a practical test to indicate the stage of the disease and response to treatment. The diastolic pressure is known as the "minimum tone pressure," because it is the pressure registered by the sphygmomanometer at the moment when the auscultatory bruit disappears with decompression of the brachial artery. The essence of the test is that, when the diastolic pressure is registered, the administration of adrenalin in hypodermic doses of 1 mgm. will be found, if observations are taken at five-minute intervals, to bring the pressure down to zero in an uncured case of beriberi. That is to say, the auscultatory murmur will persist during complete relaxation of the pressure of the artery as long as the patient is under the influence of adrenalin.

Cardiac attacks.—Most cases die from paresis and over-distension of the right heart, complicated and aggravated by oedema of the lungs, diaphragmatic paralysis, hydrothorax or hydropericardium. Sudden cardiac failure (termed by the Japanese "Shōshin") is often contributed to by the co-existence of pleural effusion, hydropericardium, paresis of the diaphragm, over-distension of the stomach by food or gas, and, above all, by oedema of the lungs. It can readily be understood how any additional obstruction of this description would still further tax the dilated, enfeebled heart and determine the fatal issue.

Subacute cardiac beriberi, as described by Casanova (1946), is really cardiac damage in patients suffering from the disease in a chronic form. Radiologically there is gross right-sided cardiac enlargement with striking pulsation in the pulmonary conus and the aorta. There is no uniformity about the cardiographic tracings in this type. Generally the P wave is accentuated. The indications are those of a sinus tachycardia with marked delay of passage of cardiac impulses through the ventricles. Administration of digitalis to this type increases the pulse rate.

Secondary beriberi. *Beriberi manifestations produced by other diseases.*
Alcoholic beriberi.—It has long been recognized that alcoholic neuritis resembles in many respects the paraplegic form of beriberi. It resembles it so closely that in recent years the idea has gained ground that this resemblance is more than fortuitous, and that in both conditions there is an antecedent deficiency of vitamin B₁. The theoretical considerations advanced by Shattuck have led to the recognition of a variety of intestinal conditions in which polyneuritis may occur, such as gastric carcinoma, chronic intestinal obstruction, and ulcerative colitis, and, in the opinion of some observers, all these should be included under the heading of secondary beriberi. Cases have been reported of alcoholic addicts with congestive heart failure and polyneuritis who have recovered completely after treatment by rest, a high-calorie diet, and vitamin B₁.

Multiple factors are probably concerned in the production of alcoholic beriberi, including defects in diet and assimilation acting in conjunction with increased tissue requirements for vitamin B₁, due to an increased rate or type of metabolism. Many cases of alcoholic neuritis have now been cured by long-continued injections of aneurin. Weiss and Wilkins (1936) described the clinical syndrome of cardiac beriberi associated with alcoholic gastritis, which resembles the classical form of the disease. Alcohol is a significant factor in precipitating beriberi, not only because it supplies calories without B₁, but also because its metabolic effect is similar to that of pure carbohydrate. In response to aneurin the cardiovascular disorders disappear before the polyneuritis. Dysfunction of the cardiovascular system resulting from unbalanced food intake is a disease of regular occurrence in America. Tachycardia, followed by bradycardia, and gallop rhythm with electrocardiographic changes are considered to be characteristic of the beriberic heart.

Strauss thought that the *polyneuritis of pregnancy* may be of the same nature when pernicious vomiting occurs. In *diabetic neuritis*, also, it has been shown that the injection of aneurin exerts an influence upon carbohydrate metabolism.

Infantile beriberi.—This form is common in Egypt, the Philippine Islands, South China and certain Pacific Islands, and causes a high infantile death-rate. In the Philippines especially it was a terrible scourge, accounting for 16,500 deaths annually, or 28.1 per cent. of total deaths in infants under one year. It is not necessary to regard it as resembling adult beriberi in miniature, for it differs in many essentials. The disease often occurs in the rainy season. It is never seen in Caucasians, rarely in half-castes, and should be regarded as strikingly a disease of poverty. It usually affects breast-fed infants of mothers who are either themselves victims of beriberi or subsist on a diet poor in vitamins. In Hong Kong Fehily stated that in initial, subacute and acute infantile beriberi breast-feeding immediately antedates the symptoms, but in the chronic form breast-feeding might have ceased weeks or even months previously. Removing the infant from the breast, or administering an extract of rice bran, usually leads to a rapid cure.

Haridas (1937) classifies infantile beriberi into three groups, aphonic, polyneuritic and cardiac, of which the commonest is the last, but mixed forms may occur.

The disease depends upon deficiency during uterine life and after birth

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of a substance in the milk which is essential to the growth and development of the child's nervous system. In the most acute type it is children previously healthy, 1½ to 8 months old, who are usually attacked; after a series of convulsions the child suddenly dies of acute heart-failure (Fig. 70). In less fulminating cases, vomiting, dyspnoea, dysphagia, and aphonia may precede heart-failure. The child moans or whines in characteristic fashion and the beriberic cry is diagnostic. Ptosis is also common. The blood pressure is low. The total acidity and free hydrochloric acid in the gastric juice are reduced. Occasionally, chronic cases are seen in which progressive weakness and wasting, with periodical attacks of vomiting, occur. In neither form has true paralysis been noted, except that underlying aphonia which was ascribed by Kubo in Japan to a paralysis of the left recurrent laryngeal nerve from pressure by a dilated left auricle. The knee-jerks are usually absent.



Fig. 70.—Infantile beriberi. Nauruan child in convulsions. Note general anasarca. (Dr. G. W. Bray.)

Pekelharing and Winkler found degeneration of the laryngeal nerves and muscles at autopsy. In one there was also degeneration of the muscles of the tongue.

Mortality.—The mortality in beriberi varies in different epidemics and in different localities. On the whole, it is greater in low than in high latitudes, in the dropsical than in the atrophic forms, in the acute than in the chronic. In some epidemics it is as high as 80 per cent. of those attacked; in others as low as 6 per cent., or even lower.

Wernicke's encephalopathy.—The combination of ataxia, clouding of consciousness and ophthalmoplegia was described by Wernicke in 1881 as acute superior hæmorrhagic polioencephalitis. Subsequently this syndrome was associated with chronic alcoholism; from 1938 onwards its connection with vitamin B₁ has been suspected and a similar condition had been described in nutritional disease of silver foxes in America. The accuracy of the forecast was shown by the outbreaks which occurred in

prisoner-of-war camps in the Far East. A review of 52 cases has been made by Wardener and Lennox. Other descriptions are by Spillane and Dean Smith. There were 21 deaths and the diagnosis was established at autopsy by demonstration of hæmorrhages in the mamillary bodies of the brain. In its clinical and pathological manifestations cases show no resemblance to any form of infective encephalitis. From the rapidity with which it responds to injections of aneurin this encephalopathy appears to be produced by an acute deficiency of vitamin B₁. The predisposing causes are dysentery, diarrhoea, failure of adaptability to a rice dietary, febrile conditions such as sepsis from gunshot wounds, and chronic malaria. The first symptom is the persisting anorexia, followed a week later by vomiting and nystagmus. Then the full picture develops of miserable inactivity, insomnia, disorientation, non-co-operation, semi-coma and severe oculomotor palsy. The eye symptoms consist of wavering of visual fields on looking to the side, diplopia, photophobia, insomnia and giddiness. In the alcoholic type there are often residual psychotic changes and sometimes glossitis; pellagrous skin eruptions and manifestations of ariboflavinosis may coexist. In the deficiency type other forms of beriberi are associated in 90 per cent.

In the eye horizontal nystagmus is the earliest sign; in a quarter of the cases there is paralysis of the external rectus, sometimes complete disconjugate wandering, loss of visual acuity, papilloedema, ptosis and retinal hæmorrhages. Other disturbances of the central nervous system consist of lesions of the trigeminal, facial, auditory and glossopharyngeal nerves.

The *pathology* has been described by Campbell and Biggart. Occasionally there are visible hæmorrhages. On section pathognomonic lesions are seen. There are foci of congestion and hæmorrhage scattered symmetrically in the grey matter of the brain stem and hypothalamic regions. The mamillary bodies are nearly always affected. The lesions show specific selectivity for the vegetative centres, being most severe in the lateral horns and Clarke's nuclei at the thoracic level. Thrombosis is rare, but there are numerous perivascular hæmorrhages with widespread degenerative changes throughout the brain. *Treatment*.—There appears to be unanimity that, directly the diagnosis is established, symptoms are relieved by injections of aneurin, 50–100 mgm. parenterally, daily.

Nutritional retrobulbar neuritis.—The frequency of this serious condition in prisoners of war in Japanese hands necessitates its inclusion in this chapter. It manifests itself by the loss of visual acuity with disorders of perception, such as shimmering and flickering of images. According to Dean Smith there is usually some degree of pain in 54 per cent. and the consciousness of a central blind spot is a spontaneous complaint in 6.5 per cent. Photophobia is not common and no corneal or conjunctival lesions are seen. On the other hand *visual acuity* is not a good guide. A visual acuity of less than 6/60 is found in a small proportion, mainly in men, but a central or paracentral scotoma is found in all and is larger for red than for black and white with constriction of visual fields. Ophthalmoscopy reveals degenerative pigmentary changes around the macula in 10 per cent. and optic atrophy in 1 per cent. Temporal pallor of the disc in 25 per cent. indicates that the condition

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was progressing slowly. Whitfield (1947) states that the connection with the beriberi syndrome was unequivocal. The majority had cardiac beriberi, a considerable proportion showed the orogenital syndrome and, in some, burning feet suggesting a pellagrous tendency. In a small group which were treated with multivitamin capsules—riboflavin, pyridoxin and pantothenic acid in addition to A, B₁ and nicotinic acid, all except one improved.

Burning Feet.—"Chachaleh" (Somaliland); "Barasheh"; "Kalerichal" (Tamil); "Gopalan syndrome"; "Dysæsthetic phenomenon"; (Spillane). Pyralgia; Melalgia.

This is a very chronic condition which had been recognized in Malaya, British Guiana, West Africa and Somaliland for many years. Buchanan reported on a series of over 100 cases from Somaliland. Painful or burning feet constitute the most frequent and disturbing manifestation of malnutrition in Japanese prison camps. It is doubtful whether it should be included with the beriberi or with the pellagra syndromes. Its affinity to the latter is shown by the fact that it is mentioned by Casal and is recorded by Jansen in 1787, and was seen again in the Spanish civil war. It is doubtful whether the primary lesion resides in the nerve tissue or in the vascular supply. Before the last war it was well described by Kingsbury in Malaya. Moore, Scott, Landor and Pallister have also described neurological symptoms (weakness, ataxia, inco-ordination and loss of visual and auditory acuity) associated with burning feet in that country.

The syndrome commenced with deep aching in the sole of the foot, spreading, like a toothache, to the toes and instep. The sufferings of the victims could hardly be exaggerated. Soon the whole foot was involved with the most acute "pins and needles." The pain was usually worse at night; most of the affected prisoners slept with both feet outside their blankets, but the condition progressed with excruciating bouts of shooting pains up and down the feet and calves and it sometimes took months to develop. Sometimes, too, the palms of the hands were involved. Shortly after onset delimited hyperhidrosis of the affected parts appeared and was gradually replaced by ascending skin analgesia with complete insensibility to pin-pricks and cotton wool. First the ankle jerks, then the knee jerks, after some increase, slowly diminished. No loss of superficial reflexes was noted. Advanced cases showed loss of passive movements and sensation and co-ordination became rapidly inaccurate. Many developed retrobulbar neuritis and most exhibited associated ariboflavinosis phenomena, such as eczematous scrotal dermatitis, glossitis and angular stomatitis (Whitfield, 1947).

Diagnosis.—Usually the diagnosis of beriberi is not difficult. Multiple peripheral neuritis occurring as an epidemic, or in a place or ship in which the disease has occurred on some previous occasion may, as a rule, be set down as beriberi. Sporadic cases may be difficult to diagnose, especially if there is a history of alcoholism, of malaria, or of drugging with arsenic. The presence, actual or past, of cedema—especially of cedema over the shins—and palpitations and other evidences of cardiac implication, are significant of beriberi. In the atrophic or paralytic type the *jongck* or "squatting test" is very useful. The patient is unable to assume, or rise from, a squatting position with his hands on top of his head. It must be borne in mind that slight anæsthesia of the prætibial skin area, slight cedema of the same region, slight hyperæsthesia of the calf muscles, and, perhaps, impairment or absence of knee-jerk may be the only signs. *Rheumatism is rare in the tropics.*

Pyruvic acid determination in the blood is of diagnostic value. In acute beriberi the blood contains about 2 mgm. per cent.; in untreated chronic cases 1.5 mgm. per cent. and in those injected with aneurin about 0.5 mgm.

Meyers introduced two new tests for the diagnosis of cardiac beriberi. The first is the development of, or increase in, an audible sound in the antecubital space after subcutaneous injection of adrenalin. The second and more important is the estimation of diuresis after the fasting patient has drunk a litre of water. The volume of urine passed every half hour is charted for four hours. A normal person excretes all the fluid, but in beriberi there is water retention; this should disappear after treatment with aneurin. (Volhard's diuresis test.)

Differential Diagnosis.—Cases have been diagnosed as cardiac disease, tabes dorsalis, muscular rheumatism, progressive muscular atrophy, ascending spinal paralysis, and have, over and over again, been relegated to that refuge for ignorance, malaria. There should be no difficulty in distinguishing beriberi from tabes dorsalis, by the Argyll-Robertson pupil and the positive Wassermann reaction. In both paraplegic beriberi and locomotor ataxia, Abadie's sign (absence of pain on compressing the tendo Achillis) is present.

Beriberi can be differentiated from *alcoholic neuritis* by the tremors and mental disturbances which are generally obvious; from *arsenical neuritis* by the pigmentation, the diarrhoea, and digestive disturbances, and by the hyperkeratosis of the palms and feet that is apt to occur in this intoxication; from *chronic lead-poisoning* by the blue line on the gums, the wasting of the arm and leg muscles which are most in use, the characteristic sparing of the supinator longus, and the basophilic stippling of the red blood-corpuscles; from *lathyrism* by the presence of the knee-jerks and the absence of muscular hyperæsthesia in this affection; and from triorthocresyl phosphate poisoning (ginger or jake paralysis) which causes a flaccid form of motor paralysis. The differential diagnosis from heart disease, chronic nephritis, and ancylostomiasis is sufficiently obvious.

It may be necessary to differentiate Korsakoff's syndrome and Landry's paralysis.

Famine œdema (nutritional cedema) is more pronounced than cedema of simple starvation, and other causes than mere lack of sufficient nutriment are at work. It is most pronounced in the feet and legs, and marked muscular weakness and alimentary-tract disturbance are common. It was common when there was a shortage of fats, as in Central Europe during the 1914-18 and 1939-45 wars. In Java and Haiti a form of malnutritional cedema was prevalent among individuals whose diet was inadequate, and amongst infants fed on a preponderantly starchy diet over a long period. In these a generalized dropsy, similar to famine cedema and cedematous beriberi, is observed. Famine cedema was extremely common in Japanese prison camps in Singapore and Java during the recent war. There ensued considerable confusion with cardiac beriberi. The "hungerœdem" of the Dutch was synonymous with wet beriberi of the British medical staff. There can be no doubt that both existed, but that the former was most common and rapidly disappeared on an adequate dietary. This condition is probably not due to vitamin deficiency, but to lack of albumin and fats in the food. The primary effect is reduction in the plasma-protein, and is especially the case with deficiency of animal protein which results in a decrease in the plasma-albumin fraction with ever increasing globulin percentage. Oedema takes place when the plasma protein level falls below 4-5 grm. per 100 ml. (Himsworth).

Later the total protein is reduced and there is inversion of the normal

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albumin-globulin ratio, accompanied by disturbances of osmotic relationship and water retention within the tissues.

The normal value of plasma proteins are :

Total protein . . .	6.5 to 8.5 grm. per 100 ml.
Albumin	4.2 to 5.7 grm. " "
Globulin	1.8 to 3.0 grm. " "

TREATMENT

The first and most important thing is the diet. It should be high-protein with high vitamin content to provide 120–150 grm. of animal protein per day with restriction of salt and fluids. From this, rice, especially white rice, should be eliminated, and some article rich in vitamins—such as beans, peas, peanuts, barley, wheaten flour (not overmilled), or oatmeal—substituted. Apart from other considerations, rice is a bad food for beriberics ; it is too bulky. Eggs are valuable sources of the anti-beriberi factor, which is not destroyed, even when they are dried. Yeast has curative properties ; the extract known as *marmite* may be given in doses of 1.5 grm. daily. Animal food, including fat and milk, must enter into the dietary for general nutritional purposes. The worst cases, particularly if there is any sign of serious cardiac implication, should remain in bed : but the mild cases had better spend the greater part of the day in the open air.

In cardiac cases, with a view to diminishing to some extent the bulk of blood in the vessels and heart, the seriously affected patients should take little fluid, and keep the bowels free by full and repeated doses of some saline aperient. Small doses of digitalis or strophanthus seem to do good. Should signs of acute cardiac distress appear, full doses—3, 4, or 5 drops of the 1 per cent. solution—of nitroglycerin are indicated, and intravenous injections of ouabaine (a French preparation of strophanthin), $\frac{1}{2}$ to $\frac{1}{4}$ gr., may be given. Should signs of cardiac distension and failure persist and increase in spite of these means, there must be no hesitation in bleeding the patient, taking, if it will flow, eight or ten ounces from the arm or (this failing for any reason) from the external jugular.

The introduction of vitamin B₁ (aneurin or thiamin) as a therapeutic agent has revolutionized the treatment of beriberi, and its dramatic effects are best observed in the acute cardiac cases when given in big doses. Hawes, Monteiro and Smith emphasized that it is in the acute attacks which break out without any previous warning that its effects are best seen. Wilkinson (1938) recommended immediate intravenous injection of 50 mgm. of aneurin, to be repeated two or three times in twenty-four hours until serial skiagrams show that the heart has become reduced to normal limits. In moribund patients the injection has been made direct into the jugular vein with spectacular success. There are two crystalline preparations in use for injection, *Betaxan* (Bayer) and *Benerva* (Hoffman, La Roche). These preparations normally contain 2 mgm., but the strong or "forte" dose is 10 mgm., of crystalline aneurin per ml.

In advanced paraplegic cases the results of aneurin treatment are by no means so satisfactory ; whereas pain and subjective dysesthesia are relieved, the nervous signs take a long time to disappear. In the Far East,

especially in China, results are disappointing, because patients inevitably relapse when they return home and resume their polished rice dietary.

Breast-fed beriberic infants should be removed from the mother and handed over to a healthy wet-nurse, or placed on the bottle. Sometimes this is impracticable; in such cases in the Philippines a preparation of extract of rice-polishings, known as "tiqui-tiqui," has the reputation of being wonderfully efficacious. It is given to the extent of 5 ml. a day in 20-drop doses every two hours. At the end of twenty-four hours the most alarming symptoms disappear, and the child is well in three days. If the case is a very severe one, double doses should be given, and the tiqui-tiqui continued so long as there is any aphonia. Under modern conditions obviously aneurin is indicated. How found that in the most acute cases one injection of 5 mgm. aneurin, followed by 3 mgm. by mouth, sufficed. In chronic cases oral administration is satisfactory.

Prophylaxis.—In institutions under Government control, or in conditions in which it can be successfully enforced, there should be a stringent rule against the use of overmilled rice. To legislate against the use of white rice in countries in which rice is the staple food would not be politic, and could only lead to opposition and defeat the object in view; but the authorities, by educative methods and in other ways, can do much to eradicate gradually any prejudices there may be among the natives against undermilled rice.

CHAPTER XXVII

PELLAGRA

Synonyms.—Mal de la Rosa; Mal Rosso; Alpine Scurvy; Asturian Rose.

Definition and description.—An endemic disease of slow evolution, which is undoubtedly connected with dietetic deficiencies, characterized by a complexity of nervous, alimentary and cutaneous symptoms, which make their first appearance during the spring months (sometimes the autumn), and recur year after year at the same season, remitting more or less during the winter months. It is for the most part confined to the poorer classes, especially agricultural labourers. The more distinctive features are (a) a remitting dermatitis of the exposed parts of the body; (b) marked emaciation; (c) profound depression alternating with mania; (d) a terminal confusional insanity.

Since 1912 sporadic cases of the disease have been reported in the British Isles. Many of these fall into the category of what is known as "secondary pellagra."¹

Geographical distribution.—*Europe*: Pellagra is found in Northern Portugal, in Spain, in Italy, in the south-west of France, sparingly in Denmark and in the British Isles, in the Austrian Tyrol, in Hungary, Croatia, Dalmatia, Bosnia, Yugoslavia, Bulgaria, Turkey, Greece, Corfu, Roumania, Bessarabia, Kherson, Poland and Transcaucasia. A few cases have been reported from Germany. *Africa*: Algeria, Tunis, Egypt, Sudan, the Red Sea coast, Rhodesia, Nyasaland, and among the Kaffirs and Zulus. It has also been recognized in Tanganyika, Kenya and on the Gold Coast. *Asia*: It has been reported from Asia Minor, Armenia, Syria, North Behar and Deccan in India, the Malay States, the Philippine Islands, Japan, China and Korea. An outbreak of pellagra was recorded in Nanking in 1920, in Shanghai in 1940, and by French observers in Szechuan. Yu reported typical cases in Manchuria. It was especially prevalent among Turkish troops and Armenian refugees in Palestine and Syria during the 1914-18 war. *America*: Canada (since 1914), the United States, Mexico, Central America, Brazil, the Argentine, Barbados, Jamaica, and probably other West India Islands. *Australasia*: Pellagra has been reported from New Caledonia and Australia (Melbourne).

Pellagra in Great Britain.—According to Stannus, the first authentic case in Great Britain was reported by Howden in 1866, the second by Brown in 1906, and the third by Brown and Low from Shetland in 1909. In 1912 a series of six cases was investigated by Sambon and Chalmers, and in 1913 Box published his two famous cases in St. Thomas' Hospital. Since then it has come to be generally recognized that pellagra is found sporadically in lunatic asylums and other institutions, in subjects of general malnutrition. In the statistics of the Board of Control in the period 1913-1918, 45 deaths were noted. In 1922 there

¹ For more detailed information the reader is referred to the masterly summary by H. S. Stannus in the *Tropical Diseases Bulletin*, 33, 10-12, and 34, 8.

were 21 deaths, mostly from the Lancashire Mental Hospital, Rainhill, and during the period 1913-1928 there were 104 deaths from pellagra amongst asylum inmates.

In Europe the disease invariably appears in manifest and epidemic form during the spring and autumn quarters, the spring outbreaks being by far the more severe, the autumnal recurrence often inconspicuous or lacking. In Egypt, according to Chalmers, there is a spring invasion in April and May, and an autumn recurrence in November. In Nyasaland, according to Stannus, pellagra seemed to prevail chiefly during August, September, and October, which are the spring months in the southern hemisphere, and again, though to a lesser extent, in January, February, and March (fall recurrence). In the United States of America, owing to the vast extent of territory and great variety of climates, the periodical incidence of the disease is necessarily different in different sections. In the Northern States, as in Europe, the disease exhibits the usual well-marked double incidence, the spring outbreak occurring in May and June, the autumnal one in September and October. In the far south the disease may appear as early as January, and may be met at any period of the year. In Barbados it seems to prevail more or less from May to October or November. While the wide range of pellagra throughout the world might suggest that climate exerts no special influence, the very definite seasonal periodicity shows that climatic factors play an important, though indirect, part.

Sex.—Both sexes are liable, but in different places the disease exhibits a very different predilection for the one or other sex in accordance with the occupations and habits of the people. In the United States it is said to be more prevalent in women from 17 to 40 years of age; the debilitating effects of menstruation, pregnancy, and lactation are held to be predisposing and determining factors.

Age.—Pellagra is a disease of middle age, the majority of cases occurring between twenty and fifty. Within the endemic centres children are attacked, and infantile pellagra is common in West and East Africa and Southern China (*see p. 406*).

Occupation.—The disease prevails most of all among field-labourers. The inhabitants of towns, even of those in the very heart of intensely pellagrous districts, usually enjoy immunity. Although it has been stated that pellagra is rare in the Jewish race, it is quite common in Palestine, where it is confined to the poor town dwellers, whilst agricultural labourers for the most part escape.

Diet.—The flooding of some of the Southern States in America by the overflowing of the Mississippi in 1927 afforded a practical example of the dietary factor. Pellagra, though common in these States, depends to a great extent on economic conditions. The diet of molasses and cornmeal contains very little of the pellagra-preventive factor, and only when the financial conditions allow can milk, eggs, etc., be purchased. The failure of the cotton crop meant poverty, reduced food, and pellagra.

Pellagra and maize.—The general opinion was that pellagra appeared soon after the introduction of maize into Europe, and that it advanced *pari passu* with the extension of maize cultivation and with the more general adoption of the new cereal as an article of food. For these and other reasons maize was held by many to be the causative agent of pellagra, just as a certain condition of rye was known to be the cause of ergotism; and, as in the latter case, various theories have been propounded to explain the operation of the assumed cause.

Deeks in 1912, and Funk in the same year, suggested that pellagra was a disease produced by a deficiency in diet. In 1914 Goldberger and Wheeler fed a squad of eleven prisoners on a rich carbohydrate diet deficient in proteins. After five months, six developed cutaneous symptoms suggestive of pellagra (the first lesions consisted of an erythematous patch on the scrotum). An experiment in the converse direction also proved successful, for, by substituting a rich protein diet for one consisting in great part of carbohydrates, they succeeded in banishing pellagra from an orphanage asylum in which up to that time pellagra had been in evidence. In 1917 Goldberger successfully disposed of the "infection theory" by obtaining sixteen volunteers who attempted to infect themselves by ingesting skin scales and naso-pharyngeal secretions of pellagrins over a period of six months. They remained quite healthy. In 1919 the commission which investigated the prevalence of pellagra amongst the Turkish prisoners in Egypt attributed the cause to a primary deficiency of "biological proteins" (B.P.V. = Biological protein value).

Although epidemics of pellagra are found usually amongst maize-eaters, many isolated cases arise under a variety of circumstances. It appears that the true cause of pellagra is much more complicated and consists in the disturbance of a delicate chemical balance between certain toxins, present in relatively large amounts in maize, and some essential dietary factors. Nicotinic acid and tryptophane are two of the latter, but the chemical composition of the poison, or poisons, is unknown. Analogues of nicotinic acid can produce pellagra-like effects in animals, but it is uncertain whether these are the poisonous substances present in maize. The problem of pellagra is therefore an intricate problem of biochemical balances.

The not infrequent occurrence of *secondary pellagra* is probably due to non-absorption of the necessary vitamins by a diseased or non-functioning mucosa.

Pathology.—The pathological features essential to pellagra may be obscured by complicating diseases, such as bacillary dysentery and tuberculosis. The morbid anatomy is neither constant nor characteristic; for this the chronicity of the disease, the variety of the symptoms, and the many intercurrent affections which may arise are responsible.

A constant and striking feature is the great emaciation. The viscera show chronic degenerative changes, particularly fatty degeneration, and a characteristic deep pigmentation. The intestinal walls are greatly attenuated through wasting of their muscular coat, while at the same time the mucous lining is hyperæmic and, not infrequently, ulcerated. The liver and spleen are usually atrophied. The suprarenal capsules may be atrophied and the cortex may be black, while the medulla is whitish and may be the seat of hæmorrhages. The heart is usually in a condition of brown atrophy and weighs only 2-3 ounces.

There may be milkiness, thickening of the meninges and sometimes cedema of the brain. In the cord the lateral columns and the crossed pyramidal tract are especially implicated, but the direct cerebellar tracts usually escape. The anterior cornual cells are frequently atrophied and deeply pigmented. The posterior columns do not escape, the median portion often being degenerated. The degenerative changes in the lateral columns are chiefly in the middle and lower thirds of the dorsal region, those of the posterior columns principally in the cervical and upper dorsal region. The cerebro-spinal fluid shows little change; there is usually no increase in the globulins.

Mott remarked on the changes in the cerebrum, cerebellum, pons, medulla, and spinal cord that in none of the sections is there any evidence of meningeal or perivascular infiltration with lymphocytes, plasma cells, or polymorphonuclear leucocytes. All the changes were like those produced by a chronic toxæmia, possibly in the manner already suggested. The posterior spinal ganglia cells



Photo: Dr. A. D. Blandford

PELLAGRA RASH ON FEET

Dorsa of feet had been exposed to sun in area between turned-up trousers and uppers of shoes.

PLATE VIII

show, in varying degree, a pronounced chromatolysis, swelling of cells, and disappearance of Nissl's granules, and all the anterior-horn cells and their homologues in the medulla and pons a varying degree of perinuclear chromatolysis. With the Marchi method, degeneration is most definite in the column of Goll. In most cases the afferent tracts are more affected than the efferent. There is usually marked chromatolysis of the cells of Clarke's columns. The Betz cells of the cortex and the cells of Purkinje showed similar changes, but in a lesser degree. There is also atrophy of pyramidal cells in that part of the layer which lies on the ventricular surface of the fascia dentata. In short, the changes in the central nervous system resemble those of central neuritis (Adolf Meyer) or of subacute combined degeneration of the cord. Greenfield and Holmes thought that the pellagrous changes differed from those of the latter in the absence of gross distension of the myelin sheaths.

Shattuck drew attention to the close ætiological relationship between beriberi, Korsakoff's syndrome, pellagra, central neuritis, and subacute combined degeneration of the cord.

Central neuritis, which is undoubtedly allied to pellagra, was first described by H. H. Scott on sugar estates in Jamaica, and it was subsequently found in Sierra Leone and Nigeria. The central nervous lesions are widespread; the peripheral nerves are demyelinated and the posterior root ganglia of the spinal cord show degenerative changes. The medulla, cerebellum, basal ganglia and optic nerves are also affected.

Clinical pathology.—There is hypochlorhydria in 40 per cent., and quite frequently achlorhydria. In advanced pellagra there is usually anæmia, which is of macrocytic and hyperchromic type in about 50 per cent.: microcytic in the other half. The total leucocyte count is not disturbed, though there is often lymphocytosis. An indirect van den Bergh reaction is usually present in the serum. There is no change in the corpuscular fragility; the plasma albumin is diminished.

The fæces are pale, milky, soapy, sometimes steatorrhœic. The urine is generally alkaline and may rapidly become ammoniacal. It may also contain tube-casts, traces of albumin and, usually, indican. Much attention has recently been drawn to the excretion of coproporphyrin (porphyrinuria) and speculations have been made regarding its significance. Some regard it as indicating faulty liver metabolism; others as the result of abnormal intestinal absorption. As stated by Beckh and Ellinger, it is specially found in secondary alcoholic pellagra, but Spies, Cooper and Blankenhorn showed that the amount of coproporphyrin in the urine appears to be proportional to the nicotinic acid intake.

Symptoms.—The cardinal signs of pellagra constitute the well-known diagnostic triad: "diarrhœa, dermatitis and dementia." The course is generally long and irregular, one of repeated exacerbations and periods of quiescence. The initial symptoms are composed of mingled psychical and digestive disturbances which may recur for years without the appearance of skin eruptions. The patient is pale, has a peculiar lifeless staring look, with dilated pupils, and complains of headache, giddiness, and vague but often severe pains in the back and joints. The scleræ are bluish and leaden coloured. The eyelids move sluggishly; the complexion is muddy. The character changes, becoming irritable, and at the same time stupid and morose.

Observations on children in pellagrous families in the United States show that many have clinical signs of pellagra. They are below the normal weight and height for their years; they make slow progress at school, show lack of interest, inability to concentrate and have poor appetites. Their hearts are irritable and they may have tachycardia.

The earliest signs of a pellagrous tendency are difficult to define, as there are probably a great many people who suffer from chronic ill-health and are really in the pre-pellagrous state. This tendency may manifest itself by a peculiar stomatitis with erosions at the angles of the mouth (angular stomatitis) (Plate IX). There may also be an atrophic condition of the lips (*perlèche*) or cheilosis (see p. 413). The pellagrous process may not proceed beyond this stage. On the other hand, it may be progressive and advance to a fully developed syndrome. Then the gums may be swollen and bleed easily, a condition which gave rise to the term "Alpine scurvy." There may be eructations of gas, nausea, and vomiting. The appetite is variable. The epigastric region and, sometimes, the lower abdomen are tense and painful. Constipation may be present, but in rare instances there is diarrhoea of pale fermenting stools resembling those of sprue. The scrotum is often eczematous (Fig. 72).

The pellagrous rash.—Most observers regard the skin lesions of pellagra as early manifestations, but they are symptomatic of the underlying constitutional disturbances. At first an erythema, not unlike a severe sunburn, is observable on the parts of the body which are, as a rule, unclothed and exposed to the sun (Plates VIII, IX). The eruption is symmetrical and characteristic. It appears suddenly, first on the back of the hands and feet, then on the forearms, legs, chest, neck, face, and, it may be, on the scrotum or on the female genitalia, anus and other regions subject to mechanical irritation. Patches of erythema are irregular in outline and intensity. Very characteristic is a symmetrical eruption behind the mastoid processes, a ring or collar round the neck (Casal's necklace), and a butterfly patch over the bridge of the nose resembling lupus erythematosus. The affected area is swollen and tense, and the seat of burning or itching sensations which become particularly acute on exposure to the sun. The congestion disappears completely, but temporarily, on pressure. Petechiæ are common on the affected parts; blebs with clear, opaque, or blood-stained contents of feebly alkaline reaction may form. The eruption usually lasts about a fortnight, and is followed by hyperkeratosis and desquamation, which leaves the skin rough, thickened, and permanently stained a light sepia. This is especially marked on the back of the hands and on the elbows, thus constituting recognizable evidence of pellagra. Hyperkeratosis may occur on the soles of the feet and as diffuse thickening over the knuckles. In severe cases the skin over a large area of the body comes to resemble that of a roasted turkey. Ichthyotic changes sometimes supervene and may be more intense in winter than in summer. It is on account of this roughness of the skin that the disease was originally called "pellagra" (an Italian word derived from *pelle* (skin) and *agra* (rough)).

"Purpura provocata" may precede or follow erythema. This has a linear distribution. Hæmorrhagic stripes of considerable length have been seen, especially after exposure to the sun and after trauma. This

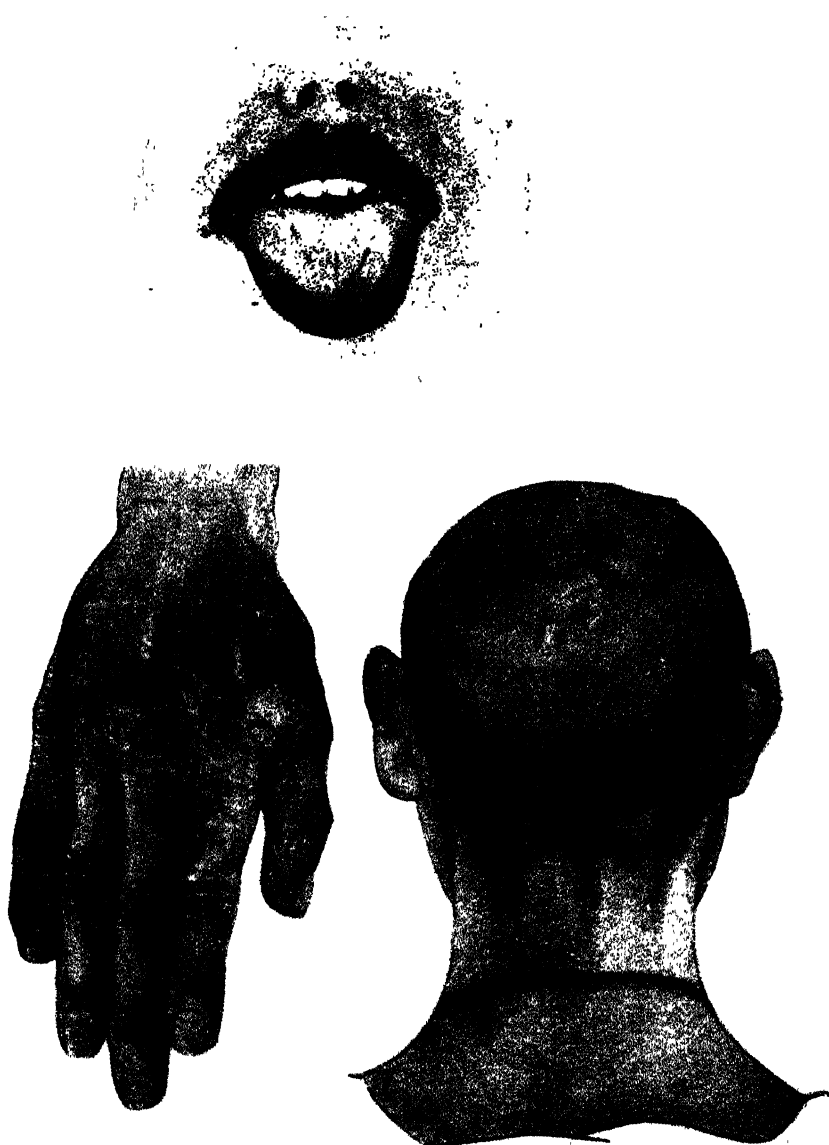
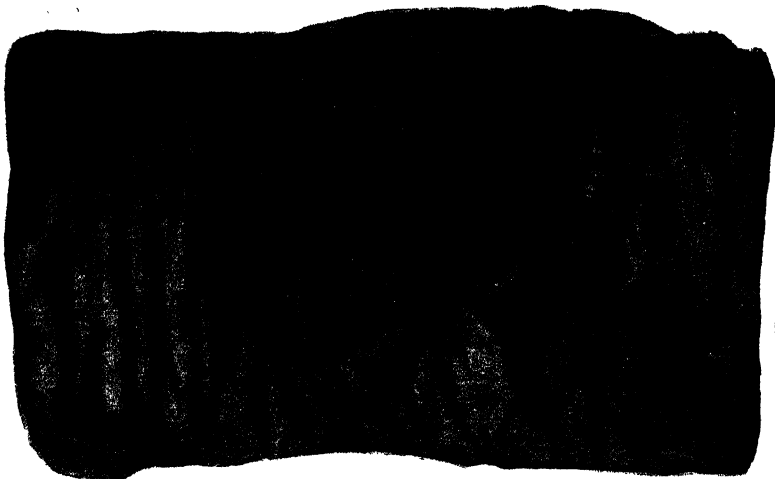


Fig. 1.—Characteristic inflamed tongue of acute pellagra with angular stomatitis.
 Fig. 2.—Early pellagrous rash, with cellular infiltration and pigmentation.
 Fig. 3.—Typical pellagrous rash over occiput and mastoid processes, with formation of “rosary” round neck.

(J. I. Enright)

PLATE IX

PELLAGRA



1



2



3

Fig. 1.—AMOEBIIC DYSENTERY. Typical patches of infiltration and ulceration of ascending colon showing "Dyak-hair" sloughs. Fig. 2.—BACILLARY DYSENTERY (Sonne infection): Acute Sonne dysentery in a child, showing bright pink hyperemia of muscular coat. Fig. 3.—BACILLARY DYSENTERY (Shiga infection): Coagulation necrosis of lower portion of ileum, showing characteristic green coloration of the destroyed mucous membrane.

INTESTINAL LESIONS IN AMOEBIIC AND BACILLARY DYSENTERY (Half nat. size) (see p. 486)

(P. Manson-Bahr)

PLATE X

phenomenon is an indication of the permeability of the blood vessels (Simons, 1946) and was observed in prisoners of war in Indonesia.

Exposure to light appears to be the precipitating factor. Ruffin and Smith showed that radiation may evoke not only skin lesions, but also associated oral, gastro-intestinal and neurological manifestations. Since injections of porphyrin can sensitize normal persons to sunlight, it has been suggested that there may be abnormal porphyrin metabolism in pellagra.

The burning sensation in the soles of the feet and palms of the hands which is such a common symptom in pellagra may be ascribed to the same cause.

Naturally, the appearances of pellagra differ considerably in different races. What is an erythema in the European becomes a blackish or purplish patch on the skin of a negro. In olive-skinned races pellagrous patches assume a sepia colour.

The pellagrous rash has to be differentiated from *follicular hyperkeratosis* or *keratosis pilaris*, which is common in ill-nourished natives in all warm climates. Dry, hard or, it may be, pigmented, papules are formed which project from the hair follicles as spiny processes. The surrounding skin is dry and rough.

Implication of the *nervous system* is indicated by tremor of the tongue, exaggerated deep reflexes, and mid-dorsal spinal tenderness. Coarse tremors of the extremities, especially of the head and the hands, are frequently noted and become more marked as the disease progresses. Muscular cramps may occur; definite ankle clonus, spasticity and extensor-plantar response are often seen. The patient suffers from obstinate sleeplessness, occasionally from uncontrollable sleepiness. He experiences great weakness, especially in the lower extremities, and is subject to peculiar attacks of giddiness, with a tendency to fall forwards or backwards. Chvostek's sign—mechanical irritability of the facial nerves—is present in the majority of cases. A very characteristic symptom is pyrosis, or a burning sensation down the oesophagus (dysphagia). This frequently creates the idea in the patient's mind that his food does not agree with him, or even that attempts are being made to poison him. The pupils are dilated and there is usually photophobia. The arms may be spastic and movements are accompanied by a coarse tremor, which is increased on exertion.

Sydenstricker (1941), in a large series of pellagrins, found that spinal cord changes were present in 6 per cent. and polyneuritis in 2·8 per cent. Spillane observed neurological signs and symptoms in individuals who had passed through several relapses. Out of 30 there were pyramidal signs in 16, absent deep reflexes in 3, reduced superficial sensation and loss of vibration sense in others.

In the early stages the manifestations are mainly psychoneurotic, but later polyneuritis may appear. General deterioration of mental and physical health may antedate the continued manifestations of the disease. Acute mania and confusion (*psychoneurosis maldica*) may herald the end. Thus pellagra may not only produce insanity, but it may result from it.

After the disappearance of the eruption, atrophic patches of skin remain in the interdigital clefts, and these, together with muscular wasting, give the appearance of washerwomen's fingers. The hands, in fact, are aged out of proportion to the rest of the body. The nails become atrophied and brittle.

As a rule, there is no marked permanent elevation of temperature, but periods of slight fever occur at irregular intervals.

Ocular changes in pellagra.—The bulbar conjunctiva is oedematous showing linear erosions on the temporal side of the palpebral aperture. Corneal dystrophy is frequent. Small ovoid opacities lie deep in the corneal stroma. Lens opacities are of three types: powder-like opacities, multiple irregular opacities, and tongue-like opacities extending from the peripheral zone towards the centre of the lens. All these are associated with acute avitaminosis B₂.

Aural manifestations.—The following defects of hearing in advanced pellagra are tabulated by de Raadt:

Vestibular hyperexcitability for cold water in 74 per cent. Spontaneous abnormalities in walking and of the Romberg test in 61 per cent. : nystagmus in 59 per cent.; heavy loss of perception of sound in 26 per cent.; tinnitus in 4 per cent.; ataxia in 16 per cent.

Progress.—Two or three months after onset the symptoms abate and although the affected skin areas remain dark and rough, the disease appears to be arrested. Next spring, however, the whole series of phenomena recurs in a more severe form. The eruption assumes a darker colour. The depression of spirits deepens into melancholia, which may have maniacal interludes, with a peculiar tendency to suicide, especially by drowning. The general feeling of weakness increases; the patient loses weight and is unable to work; his gait becomes uncertain and somewhat of the spastic paraplegic type. The tongue is tremulous. The pains in the head and back become very acute, and there may be lightning pains, cramps, twitchings, tremors, and even epileptiform seizures of the cortical type. Diarrhoea may now be troublesome.

For several years the disease may thus recur in the spring with increasing severity. The patient becomes greatly emaciated, paralytic, and completely demented. Helpless, bedridden, suffering from incontinence of urine and uncontrollable diarrhoea, covered with bedsores, and neglected, he dies from exhaustion or from some intercurrent disease.

The duration of pellagra is exceedingly variable. It may last only two or three years; it usually extends to ten, fifteen, or more.

Cases differ considerably. The obscure forms are probably much more common than the fully declared disease. They were formerly known—somewhat incongruously—as *pellagra sine pellagra*.

Ariboflavinosis.—The riboflavin deficiency syndrome is now regarded as typical of "*pellagra sine pellagra*." The following signs are characteristic of it: angular stomatitis¹ and facial lesions consisting of filiform seborrheic excrescences (dyssebacia), varying in length up to 1 mm., sparsely scattered over the face. The mouths of the sebaceous glands are plugged with inspissated sebum, giving the skin a roughened appearance, which on the shoulder, arms and legs is known as *phrynoderma* or toad's skin. The eyelids show dermatitis lesions, may be macerated and stuck together. Fissures and maceration at the angles of the mouth are seen,

¹ The term "cheilosis," or "cheilitis" applied by some writers to lesions at the angles of the mouth should be reserved for lesions on the lips.

and a degenerative crust-like formation on the epithelium of the lips, most marked on the lower. The lips, particularly the lower, frequently show a marked increase in the vertical fissuring (*perlèche*) (Fig. 71). A specific glossitis has been described: the tongue is clean, the papillæ flattened or mushroom-shaped and the colour definitely purplish red or magenta, in contrast to the scarlet tongue of nicotinic acid deficiency (Plate XVIII). An eczematous scrotal dermatitis is common as in other forms of Vitamin B₂ deficiency (Fig. 72).

The ocular manifestations are burning, lacrymation, photophobia, blurred vision, inability to see in a dim light and visual fatigue. The earliest and most common sign is circumcorneal injection and, when viewed by a slit lamp, there is marked congestion and proliferation of the limbic plexus, with the production of great numbers of narrow capillary loops. The lesion progresses to vascularization of the cornea within a week, if treatment with riboflavin is not given.

Eventually keratitis is produced, similar to that associated with acne rosacea, which is also amenable to riboflavin therapy. It is probable that ariboflavinosis is also responsible for retrobulbar neuritis, which may also be part of the pellagra syndrome (see p. 401).

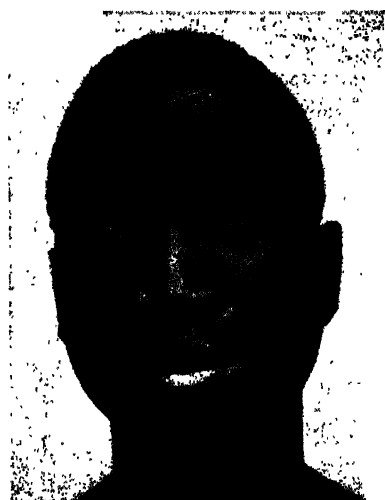


Fig. 71.—Avitaminosis B₂ in a West African negro. Characteristic facies of ariboflavinosis. (Dr. D. Fitzgerald Moore.)

Infantile pellagra.—Pellagra in childhood is very apt to be overlooked, especially in native races. The children become irritable, their skin and hair tend to lose the normal colour and glossiness, and there may be attacks of diarrhoea with transient oedema of the hands, feet, and face. After ten days or so pigmented patches appear on the skin of the extensor surfaces about the ankles, knees, wrists and elbows, and these blackened patches appear first where there is any focus of irritation or pressure. Trowell described infantile pellagra in E. Africa as a syndrome of which the principal signs are oedema, dermatitis and diarrhoea. Infantile pellagra has also been reported in American negroes, from Mexico, Cuba, Costa Rica and S. China. It has to be distinguished from malignant malnutrition (p. 420).

Pellagra typhus.—In this very acute type there are intense prostration, high temperature, muttering delirium, pronounced nervous tremor, generalized rigidity, and convulsions.

Terminal stages, pellagrous insanity.—Mental symptoms supervene in one-third to one-quarter of all cases.

It has been estimated that from 4 to 10 per cent. become permanently insane. In the United States of America pellagrins have become numerous in the lunatic asylums. The type of insanity is usually a most profound melancholia with a suicidal tendency; cases may resemble in their clinical features general paralysis of the insane. Epileptiform convulsions may occur.

The time of the appearance of mental symptoms is subject to the widest variation. They may be primary symptoms, or occur during convalescence. The mental aberrations may be characterized by profound dementia, hallucinations, and katatonia. As a rule, restlessness, vertigo and insomnia anticipate the characteristic melancholia. In general, the patients exhibit anxiety neurosis with depressive features. Psycho-sensory disturbances are common, with intolerance of bright light, colours and noises. The patients are fidgety, quarrelsome and irritable. In spite of increased motor drive, they complain of weakness and fatigue.

Not only may pellagra lead to insanity, but those insane from other causes are very liable to pellagrous manifestations. Goldberger found that in certain asylums in the United States the number of lunatics developing pellagra each year was a constant proportion of the total. In England, pellagra has been noted in lunatic asylums since 1913. Watson, in a review of the pellagra cases in the Rainhill Asylum, Lancashire, found that at the time of



Fig. 72.—Scrotal eczematous eruption in vitamin B₂ deficiency.
(Dr. D. Fitzgerald Moore.)

onset they had been resident from six months to several years.

Pellagrous encephalopathy has to be differentiated from Wernicke's encephalopathy. In the latter there is nystagmus and ocular palsies. A process of acute cerebral disturbances responding to nicotinic acid has been described in alcoholics, the aged poor, in persons depleted by illness or operation and in certain therapeutic procedures (hydration). Patients with stupor, delirium and variable reflex changes respond remarkably to the administration of nicotinic acid (Graves, 1947).

Secondary pellagra.—Pellagra due to voluntary restrictions of diet has been recognized by several observers during recent years. Mook and Weiss described the typical clinical picture in a young woman on a slimming diet; Mumford, Carley and others found it in mature women who, for some faddist cult, had been subsisting on an unbalanced dietary; Guthrie, Green, Walker and Wheeler reported similar phenomena in patients on

ketogenic régime. It is stated that hyperthyroidism predisposes to pellagra.

Pellagra in all its varied manifestations may be associated with some organic lesion in the gastro-intestinal tract, such as oesophageal stricture, carcinoma of the stomach, pyloric ulcer, pyloric stenosis, carcinoma of the ileum, stricture of the rectum, rectal polyposis, suppurating hydatid cyst, Crohn's disease, chronic amœbic dysentery, celiac disease, idiopathic steatorrhœa, or even tropical sprue. When the avitaminosis follows surgical operations on the gastro-intestinal tract, such as partial colectomy, or total or partial gastrectomy (Moynahan, 1957), is it known as *surgical pellagra*. *Alcoholic pellagra* is applied by American observers to the disease in chronic alcoholics, especially those who drink methyl alcohol. It has been suggested by Stannus, by way of explanation, that gastritis is the one common factor which supports the hypothesis that, primarily, in pellagra the fault may lie in the intrinsic factor of the gastric juice. On the other hand failure of biosynthesis of vitamins affords an explanation for the sporadic occurrence in sufferers from chronic gastro-intestinal disease. In this respect it has been found that sulphonamides are capable of interfering with the action of certain intracellular enzyme systems in which components of the vitamin B complex take part.

A case of acute pellagra with toxic confusional psychosis and skin manifestations in a man suffering from tuberculous peritonitis, following upon isoniazid (isonicotinic acid hydrazide), has been described by McConnell and Cheatham (1952). The dose was 3.5 to 5 mgm. per kg. for three months. Another instance of this sequence has been reported by Harrison and Feivel (1956) in a woman being treated by isoniazid for disseminated sclerosis and suggest possible metabolic antagonism between isoniazid and nicotamide. The latter in structure is an integral component of oxidation-reduction co-enzyme—diphosphopyridine nucleotide (D.P.N.) which plays a part in cellular metabolism. Gopalan and Srikantia (1960) show that L-leucine (20 grm) daily instigates pellagra.

Diagnosis.—Doubtful cases are occasionally encountered, but localized erythema associated with nervous, particularly mental, symptoms, great debility, and seasonal recurrence, in a person in or coming from a pellagrous district, can hardly be confounded with any other disease. The rash may be mistaken for acrodynia, erythema multiforme, dermatitis venenata, eczema solare, trade dermatitis, lupus erythematosus, syphilis, or poison-ivy dermatitis. "Crazy pavement" skin lesions, which are common on the legs of ill-conditioned natives, are not necessarily pellagrous, but are more distinctive of kwashiorkor. The gastro-intestinal disturbance and glossitis have to be distinguished from sprue; while the nervous manifestations have to be differentiated from hysteria, cerebral syphilis, general paralysis of the insane, ergotism, and lathyrism. In old people with arterio-sclerotic changes and accompanying mental symptoms, there may be lesions of hands and feet which may be a source of confusion. "Pink disease" in children may also be mistaken for pellagra, as the distribution of the skin lesions is very similar.

Treatment.—Spies, Bean, and Stone (1938) published a series of 73 cases of endemic pellagra and 99 of "subclinical pellagra," and stated that they had not

observed a single acute case that had not responded promptly to nicotinic acid therapy. Also, in a special study by Spies, Aring, Gelperin, and Stone of 60 cases showing acute mental disorder, improvement was observed within periods of ten hours to six days after nicotinic acid medication, the daily dosage being 500–1,000 μ gm. by mouth, or 100 mgm. intravenously. Further confirmation soon came from Matthews, who studied 13 cases of classical endemic pellagra maintained on a pellagra dietary. These favourable results in American pellagra have received a considerable degree of confirmation in the hands of Alport, Ghaligoungui, and Hanna in Egypt, and also of Ellinger, Hassan, and Taha (1937). They treated 15 cases with nicotinamide (Merck), the dose being 1 gm. daily by the mouth or 0.5 gm. by subcutaneous injection. On the whole, they found that acute inflammation of the tongue and ulceration of the mouth subsided in five to seven days, and the sense of taste returned in the same time; in one case colic supervened almost immediately, suggesting intolerance. Thus, nicotinamide effected great improvement in the acute mucous membrane lesions, as well as in the skin condition; on the other hand, chronic skin lesions, friction areas and chronic changes in the tongue were only slightly affected. The appetite, mental condition and general physical health were all improved. Grant and Spies recorded that pytalism, Vincent's infection and coproporphyrinuria disappeared, and Hawksley found great change in the follicular hyperkeratosis on and around the naso-labial folds.

Polyneuritis and other neurological phenomena do not respond to nicotinic acid and therefore aneurin has been recommended, but it appears to result in increased excretion of riboflavin. There are good reasons for assuming that in pellagra there are multiple deficiencies. A high calorie diet of 3,000–4,000 calories, with ample supplies of fresh meat, liver, milk and eggs, supplemented by some of the vitamin B complex, such as yeast 1–2 oz. daily, is recommended.

Since the discovery of ariboflavinosis as part of the pellagra syndrome most authorities reinforce treatment with riboflavin tablets in doses of 1–3 mgm. daily. During an outbreak of pellagra in Hong Kong, Wilkinson (1937) found the effects of intravenous nicotinamide injections almost dramatic. Patients who were disorientated, rambling in speech and unable to co-operate or swallow, became hungry and rational within 72 hours. (In acute pellagra the blood nicotinic acid was found to be 0.81 mgm. per cent. and to rise on treatment to 0.55 mgm. per cent.) In cases with rapidly increasing reduction of visual acuity, associated with concentric constriction of fields of vision, response to nicotinic acid and riboflavin daily changed the vision from 6/60 to 6/9 or 6/6 within a week.

The reaction to nicotinic acid in normal individuals is tingling and increased warmth over the malar regions and neck. Sometimes nausea, vomiting, abdominal cramps and urticaria may ensue. Nicotinic acid and nicotinamide are now dispensed in a convenient form in tablets of 80 to 50 mgm. each. In mild cases 50 mgm. are given three times daily (150 mgm.) for ten to fourteen days, and double that quantity (300 mgm.) in more severe cases. The effect upon the pellagrous rash is impressive. Sodium nicotinate (nicotinamide) has the same action, but without any unpleasant side effects. Overdosage with nicotinic acid causes some tingling and numbness of the tongue, and also in the lower jaw along the course of the inferior dental nerve. Riboflavin in maximal doses (8 mgm.) should be added in cases exhibiting signs of ariboflavinosis. The most striking and most easily observable effect of this mode of treatment is seen in the

amelioration of the tongue and mouth symptoms. It has a profound effect upon the psychology of the patient as well as on the processes of digestion and assimilation.

Treatment of infantile pellagra.—Gillman (1946) has proved that gastric extract (ventriculin) is the most satisfactory form of treatment. He further states that the addition of vitamin concentrates and iron significantly diminishes its effectiveness.

Treatment of mental symptoms.—Spies, Aring, Gelperin and Bean submitted 60 cases with mental manifestations to treatment with nicotinic acid, in maximum doses, and *coramine* (the diethylamide of nicotinic acid). These cases showed loss of memory, delirium, mania, or depression; some had a paranoid reaction. Recovery took place in all within six days. Korsakoff's psychosis and manic depressions were not influenced in the same way. Coramine is injected in doses of 2–5 ml. (ampoules of 2 ml. of 25 per cent solution) daily or given by the mouth, to a total of 20–50 ml. Those cases with spinal symptoms are singularly resistant to treatment.

Prophylaxis.—In view of the volume and importance of recent researches in this field, it is evident that the prophylaxis of pellagra is bound up in public-health measures and especially in ensuring a well-balanced protein dietary. Whether pellagra can be prevented by the prophylactic administration of nicotinic acid and riboflavin remains to be seen.

CHAPTER XXVIII

SCURVY IN THE TROPICS

EPIDEMICS of scurvy are apt to occur among gangs of coolies and labourers who are fed on an unsuitable dietary, especially in natives recruited for labour purposes and fed upon dried cereals and preserved foods, who previously had been in the habit, in their own villages, of subsisting on large quantities of fresh vegetables and fruit such as bananas.

Ætiology.—Scurvy is a food-deficiency disease. It is produced, not by general starvation, but by the absence of an accessory food factor, or vitamin, which can now be prepared synthetically and is known as ascorbic acid. This body is present in all fresh vegetables, including swedes, turnips, and onions, and in fresh fruit, especially the orange and lemon. It is very sensitive to prolonged heat and drying, and therefore is absent from tinned fruits and vegetables, and from dried legumes such as peas and beans, but re-appears directly the latter are induced to germinate. Yeast, fresh meat, and milk contain only small quantities of the antiscorbutic vitamin, and, curious to relate, according to Chick and Hume, preserved lime juice little or none at all, while preserved lemon-juice is rich in this substance.

Symptoms.—The onset of scurvy is insidious, with loss of weight, progressive weakness and pallor, and a feeling of stiffness in the leg muscles. The gums soon become affected with a swelling and sponginess of the alveolar margin. As the disease progresses, fungating masses project beyond the teeth, which loosen and fall out. The tongue swells, the salivary and lymphatic glands enlarge, and the breath becomes very foul. The skin becomes dry and rough, and very soon subcutaneous petechiæ form on the limbs and trunk, commencing *around the hair follicles*, especially on the thigh (Fig. 73). Hæmorrhages occur into the muscles of the thigh and into the knee-joint producing scorbutic



Fig. 73. Scurvy rash in sprue, showing distribution of petechiæ round hair follicles.

purpura, formerly known as *Morbus maculosus* (Welhoff). Very painful effusions under the periosteum form irregular nodes, which may break down and ulcerate. Edema of the ankles is common, and hæmoptysis or hæmatemesis may occur. Any injury is apt to cause a hæmorrhage.

Together with these objective symptoms the patient experiences cardiac distress, with irregularity of the pulse and hæmic bruits at the apex. The urine

is generally loaded with albumin. On the other hand, the digestive system is not disturbed, constipation being more common than diarrhoea. The psychical disturbances are pronounced. Headache is noted early, and delirium supervenes in the later stages. In the most advanced cases the jaw-bones generally become necrotic.

In the young the formation of a "scurvy rosary" at the junction of the costal cartilages, and separation of the epiphyses of the long bones, may occur in a variety known as infantile scurvy, or Barlow's disease.

Scurvy was formerly noted as endemic in the mine-workers on the Rand. Darling and others observed that a certain proportion of these cases was distinct in a clinical sense from those seen elsewhere. In this variety, known as *Rand scurvy*, the spongy gums and loose teeth that occur in the classical type of the disease were absent, while the heart underwent primary hypertrophy, with subsequent dilatation, suggestive of beriberi, though the neuritic symptoms of beriberi were absent, and the knee-jerks exaggerated. Rand scurvy occurred especially among gangs of native labourers when fed upon an unsuitable dietary, particularly natives from the Congo and tropical Africa, who were in the habit of consuming large quantities of fresh vegetables and fruits, and who, when in the mines, were fed on dried cereals and preserved foods. The number of these cases was very large indeed. Donaldson reported that in 1920 more than 200 cases of scurvy were treated in one hospital, of which one-third occurred within three months of entering the mines. It was found that scurvy in these natives predisposed to all kinds of bacterial infections, and especially to pneumonia. Where the diet was deficient, but not entirely lacking in vitamin C, actual symptoms of scurvy did not manifest themselves, but such individuals were very liable to bacterial infections owing to degenerative changes in the bone-marrow.

Diagnosis.—To diagnose scurvy under modern conditions is no difficult matter; but care must be taken to distinguish mild cases from pyorrhœa alveolaris. A method of diagnosis in the early stages, especially in children, was devised by Hess. The arm-band of a sphygmomanometer is placed upon the arm and inflated until the pressure reaches 90 mm., and the venous circulation is shut off. This pressure should be maintained for three minutes and then released. As soon as the cyanosis fades, an examination should be made for the petechial spots which may confirm the diagnosis of scurvy. This test depends on increased permeability of the capillary endothelium. Rotter introduced an *intradermal test* with dichlorophenol-indophenol.

Differential diagnosis has to be made from blood diseases such as leukæmia, and essential thrombocytopenia (onyalai, *see* p. 685).

Treatment.—This is chiefly dietetic. The disease, if recognized early, readily yields to a diet composed of fresh fruit and vegetables; when these are unprocureable, fresh meat can be substituted, but is by no means so satisfactory.

Raw onions are very valuable antiscorbutics, and raw potatoes and swedes have a definite curative value. Canned vegetables, except canned tomatoes, are useless.

For natives, the most valuable antiscorbutic foods are orange, lemon, and paw-paw juice, sweet potatoes, and green mealies. Incompletely fermented beer, such as the Kaffir beer, made from germinating grain, is said to be of considerable value, but this is doubtful.

Vaughan, Hunter and others reported brilliant successes in the treatment of scurvy with synthetic ascorbic acid. Many cases were reported by Schultzer, Parsons, Harris, Ray, and Szent-Györgyi; 40–100 mgm. of ascorbic acid are given intravenously to an adult for ten days with success; to infants 30–60 mgm. daily by the mouth for about fourteen days.

Germinating peas are useful when fresh vegetables are unobtainable.

CHAPTER XXIX

KWASHIORKOR

Synonyms.—Malignant Malnutrition, Nutritional Dystrophy. Diboba (Congo). M'buaki (Uganda). Depigmentation-œdème.

The first clinical description of this common tropical disease of children was given in a paper by Procter in Kenya in 1927, but it was Cicely Williams (1932) who, in Ghana, first gave it its distinctive name and described its pathology. The name is derived from the African Ga language and signifies "red man or boy" which denoted the pigmentary changes in the hair. This syndrome appears to be similar to *Mehlnähr-*

schädung, a starch or flour dystrophy, originally described in Vienna by Czerny and Keller in 1906.

It is definitely a nutritional disease which leads to damage to the liver, pancreas and, indeed in lesser degree, to all the intestinal organs. The main signs and symptoms are œdema, hypoalbuminæmia, hair changes, skin changes—diffuse depigmentation, rashes with hypopigmentation, dermatoses of external genitalia, fatty diarrhoea, mental changes, lack of resistance to cold, anorexia and stunted growth.

Aetiology.—Kwashiorkor does not appear to be caused by a single food factor, but by multiple deficiencies. Hence the association with well-known vitamin deficiency is comparatively common. Seasonal alterations in food supply may alter the pattern of the deficiency so that seasonal incidence has been noted



Fig. 74.—Kwashiorkor : œdematous form in a Fijian child of two years. (P. E. C. Manson-Bahr.)

wherever the disease occurs. In the West Indies the incidence is greatest from January to April. In the original descriptions it was emphasized that the disease was quite distinct from pellagra, but subsequently there were some doubters who thought it might be a form of "infantile pellagra." The age varies in children from six months to four years with a high mortality sometimes of nearly 90 per cent. and it is found in neglected children, especially after weaning, although Gelfand has described one in a breast-fed infant in Rhodesia. Kwashiorkor occurs mostly in ill-nourished children in the late breast-feeding, weaning and post-weaning ages. He has produced some evidence that it is not due so much to lack of proteins, as to a peculiar staple cereal diet.

In races which subsist largely on protein-deficient foods, such as cassava, plantains, yams and maize a high incidence is found. Consumption of animal protein, such as meat, fish and milk is protective. There is some evidence that vegetable protein in beans, peas and groundnuts is also protective. The particular age distribution is best explained on the basis that the period 1-4 years is one of high protein requirement and when in the African the protein intake is lowest. It is possible that deficiency of certain amino-acids, particularly methionine, may be a basic causative factor. Kwashiorkor is not found amongst the Masai, a pastoral people in Kenya, who consume milk, blood and meat occasionally.

Geographical distribution.—Although the original cases came from West Africa, it was soon recognized by Waterlow in the West Indies, in Kenya (an excellent account has been written by M. Clark (1951) in *E. African Med. J.*, 28, 6, 229, and by J. F. Brock and M. Autret *Bull. W.H.O.*, 1952, VIII, i, 1-71) and East Africa in general, Rhodesia, S. Africa, Zanzibar, Egypt, India (Hare), Indonesia (Oomen), Brazil, Fiji (P. E. C. Manson-Bahr). The pathology of the disease has been well described by Trowell, Gillman and Gillman, and also by Davies in S. Africa.

The standard work on this disease is by H. C. Trowell, J. N. T. Davies and R. S. A. Dean (1954).

Pathology is characterized by an enlarged fatty liver, necrotic foci in the pancreas and atrophy of the acini resulting in declining of the enzymatic activity of the duodenal contents. The fatty infiltration of the liver progresses from the periphery to the centre of the organ; recovery proceeding in the reverse direction. Early fibrosis is sometimes present and may lead to lobular and multilobular cirrhosis. Hepatic cirrhosis of this nature is comparatively common in Africans, whilst Waterlow in Jamaica has recorded it in a sixteen month old infant. According to workers in Africa protein deficiency can produce irreversible damage in the liver which leads to fibrosis and eventually to carcinoma of the liver.

Pancreatic changes have been observed by several workers (Gillman and Gillman, Hartz, Davies), but the pancreatic fibrosis described by the latter in adults is not seen in infants.

It has been pointed out that those organs most active in handling protein are also most vulnerable to protein deficiency. These are the pancreas, intestinal tract, liver and salivary glands in all of which lesions have been described. Much of the protein utilized by the gut, pancreas and salivary glands goes to the formation of digestive enzymes, the production of which is known to be impaired by fatty liver disease.

Clinical picture is that of a very sick, oedematous, undernourished child with depigmented scaly skin, with painful sores at the mucocutaneous junctions, mentally and bodily stunted and with diarrhoea.

Hair changes (*Achromitrichia*) are almost a constant feature, but most variable. The hairs are scanty, straight, silky to the touch, having lost their normal curl. The colour is greatly changed and may be almost white with a reddish tinge. These colour changes are usually greatest at the sides and back of the head and least on top. The eyebrows are often absent. The changes in the hair are the last to return to normal during recovery.

It takes months for the normal colour, texture and curl to be restored. Hughes in Lagos believed that *achromitrichia* is due to deficiency of pantothenic acid. Administration of this vitamin seemed to restore normal colour.

Skin changes.—Although often most marked this may be slight or absent. The skin changes may be divided into loss of pigment and dermatoses. The characteristic pigment change results in a pale reddish-brown colour, and is most easily noticed on the face where there is a tendency to circumoral depigmentation. Various forms of dermatoses are most numerous. The rash is usually localized at the extensor side of the extremities and, when peeling off, leaves a depigmented, often reddish,



Fig. 75.—Kwashiorkor in a Fijian male child of two, showing characteristic dermatosis, depigmentation and hyperpigmentation. (P. E. C. Manson-Bahr.)

oozing surface, which cracks and is known as “crazy-pavement” skin (Fig. 75). In severe cases it is well marked over the legs, and in mild ones it is best seen over the lumbar region. There is a tendency for the skin to break down, subcutaneous septic abscesses form, giving rise to deep necrotic ulcers of the skin, indescribable damage (as in the Fijian cases) and, eventually, to keratomalacia and blindness. Gangrene of the limbs may ensue also.

In Basutoland, Ground (1957) has studied the dermatoses associated with kwashiorkor. The fine, crazy-paving type also known as “alligator” or “mosaic” skin is not specific and is probably the result of chronic malnutrition. The dermatosis of kwashiorkor first appears in the napkin area or lower legs, spreading to the thighs, elbows, flexures of the knee and

The lesions commence as dark purple spots which enlarge into
 as, eventually coalescing and becoming darker.
 are probably the late manifestations of protein

deficiency and secondly lack of niacin (nicotinic acid). As the crude protein in the skin accounts probably for one-eighth of the total body protein it is not surprising that skin changes are common in kwashiorkor.

Edema shows periodic variation. Those with the most marked edema are invariably fatal. Sometimes it is confined to slight pitting of the legs. At others the child may be blown up with massive swelling of the eyelids which block the eyes (Fig. 74). The edema is sometimes deceptive and the child looks fat and plump. At others again he is a wizened little oaf with sunken cheeks, pot-belly and spindly legs. At this stage with proper feeding he may recover.



Fig. 76.—X-ray of wrist in severe kwashiorkor, showing transverse line across the radius and thin bone texture of metacarpals. (Jones and Dean, 1956.)

The edema may disappear entirely and then return.

Diarrhoea occurs at some time or other in every case, but may be intermittent. The stools are fatty, soft, semifluid and offensive. The steatorrhoea may be so pronounced as to resemble the stools of coeliac disease or sprue. An attack of diarrhoea may be the prelude to a fatal relapse. In these diarrhoea cases the liver is always enlarged, and the liver edge may be palpable, jutting down below the costal margin.

Mental changes.—The kwashiorkor child is dull, apathetic and miserable. It rarely screams or cries, but gives rise to a low and miserable whimper. It rarely resists examination and never fights or screams. It is pointed out

that, when a smile appears on the face, the child is on the way to recovery. Kahn and Falcke (1956) describe a syndrome affecting these children and which resembles encephalitis, consisting of coarse tremors, postural abnormalities, exaggerated tendon reflexes and myoclonus. The C.S.F. is normal, serum albumin tends to be low and a mild normocytic anaemia is present. The signs disappear in a few weeks on dietetic therapy.

Lack of resistance to cold.—Even in hot weather these children are cold and need woollen jerseys and thick blankets to keep them warm. When the child is most sick it lies curled in the fetal position.

Anorexia is constant and is most marked in severe cases. It is most important as the child starts to improve as the appetite reappears.

Stunted growth.—The fact that this disease retards growth makes it difficult to estimate the correct age, which is usually underestimated. The oldest child observed in Kenya was seven, but this is exceptional. Here the Kikuyu, as also the Fijians, wean their children late, sometimes after full dentition has been acquired. In general it may be said that kwashiorkor arises just after a child is weaned, or in children who are late or partially weaned. The mortality in African children is never less than 80 per cent. The ossification of the bones is delayed (Fig. 76).

As compared with European growth charts there is divergence. Whereas the weight is much the same for the first nine months, from then onwards the curve shows the maximum retardation from the second to fourth years and does not catch up to these standards by the end of the fifth year (Trowell). World maps of the distribution of kwashiorkor and of the high incidence of adult cirrhosis and primary carcinoma of the liver, overlap to a great extent and suggest that all three conditions may be produced by protein-deficient diets.

Diagnosis.—*Clinical pathology.*—There is usually difficulty in obtaining blood for investigation from oedematous infants and this is best obtained from the external jugular vein.

Serum proteins.—The average total protein is 4·7 and the mean serum protein content is about 4·2 gm. per cent. The albumin-globulin content when the average total protein is 4·17 is 52 per cent. albumin and 48 per cent. globulin. Trowell and others confirm that there is an increased globulin level.

Liver function test with bromsulphalein shows that most patients have a value below 10 per cent.

Blood counts.—The mean hæmoglobin content is 9 gm. per cent., corresponding to 3·15 million erythrocytes per c.mm. with MCV of 110 per c.μ with MCHC of 25 per cent.

Bone marrow biopsy reveals a true megaloblastic bone marrow, and a reticulocyte response follows folic acid treatment. Trowell has described macrocytic-hyperchromic (dimorphic) anaemia as the common form. This macrocytic tendency may be considered as evidence of deficiency of the vitamin B₁₂ complex.

Liver biopsy confirms the fatty infiltration of the liver in grades I and II.

Feces.—Most have steatorrhœa and the mean total fat is determined as 80–40 per cent.

Kwashiorkor has to be distinguished from hunger œdema, infantile pellagra and coeliac diseases.

Kwashiorkor still causes a high mortality which can be reduced by treatment with skim-milk powder.

Treatment.—The essence of treatment is feeding. No amount of vitamins will cure kwashiorkor. It is protein that these children need. Maize meal must be avoided. If possible the protein is best supplied in meat. Clark claims the best food is minced meat mashed up with vegetables, soup and milk, but owing to the extreme anorexia, feeding is not as easy as might appear. The best all-round food for smaller children is cow's milk when it can be procured. Dried milk preparations are not nearly so satisfactory. The Gilmans have obtained remarkable results with powdered hog's stomach (10 grm. daily for 10 days). It produces elimination of fat from the liver with increased diuresis in 24–28 hours. Choline with dried stomach is also recommended. Blood transfusions (20 ml. per kg.) into the jugular vein are repeated every day or every other day for a week or longer. This helps to build up the protein content and to repair the colloid osmotic pressure which is so important in the reduction of the œdema. It is generally agreed that return to normal dietary should be postponed till all symptoms have disappeared, and until the liver is no longer palpable. The experiences of Van der Sar in Curaçao have convinced him that too early administration of cereals with a mixed diet of mashed potatoes and vegetables results in a return of the diarrhoea. Bananas and biscuits of dextrinized flour mixed with whole milk are the first articles of solid food to be permitted. Cod-liver oil is recommended in Kenya. The weight curve and the consistency of the stools form the most important guides. Dean (1956), finding that diarrhoea in some infants was due to intolerance of carbohydrates, especially lactose, found cotton seed oil was valuable and thereon fed his patients on biscuits made in Kampala from ground nuts 150 grm., wheat-flour 50 grm., maize-flour 100 grm., cotton seed oil 25 grm., and sugar 75 grm. Thompson in Uganda recommended reconstituted dried milk powder reinforced with calcium caseinate. Soya bean also, when given alone, was effective especially when supplemented with Vitamin B₁₂ or methionine.

Durabolin (Organon Laboratories). *Novandrostenolone phenyl-propionate* is an anabolic steroid which has a positive influence on nitrogen balance and has proved to be a valuable therapeutic agent in malnutrition in children, in doses of 12·5 mgm. by intramuscular injection once in 7–10 days.

Small elevations of temperature are usually due to respiratory infections and are best combated by injections of penicillin. Extreme œdema occurs *pari passu* with muscular wasting; therefore, all patients responding to treatment lose weight in the first few weeks.

Fatty infiltration of the liver is always fatal in patients who are not treated in time. If it advances to a certain degree the changes are irreversible. Damage to the liver is usually such that, even when the patient appears to recover, this organ is impaired in adult life. In Africa it is considered that cirrhosis and carcinoma of the liver may be due to fatty infiltration in childhood.

Section III.—ABDOMINAL DISEASES

CHAPTER XXX

INFANTILE CIRRHOSIS OF THE LIVER

This disease is prevalent in Hindu children. In Calcutta, from 1891 to 1893 inclusive, infantile biliary cirrhosis—the name given to the disease—caused 1,748 deaths. Although the Hindu and Mohammedan populations of that city are about equal, as many as 1,616 of the deaths occurred in Hindus, whilst only 80 occurred among Mohammedans, the balance of the mortality being among the Eurasians and other races. The disease occurs principally in children under one year, rarely attacking those over three years. K. Rao (1941) stated definitely that it most commonly occurs in children between the ages of six and twenty-four months, that it is not found in Moslems or Europeans, and that it occurs chiefly in vegetarian families. As a rule, it begins during dentition, or about the seventh or eighth month, running a fatal course in from three to eight months. In rare cases it may commence within a few days of birth. Instead of lasting several months, its progress may be much more rapid, and terminate in death in from two to three weeks. In India it is common in Bengal, Madras, Bombay Presidency, and the United Provinces; it is more prevalent in rural districts than in towns.

Ætiology.—The cause of infantile cirrhosis is unknown. Neither alcohol, syphilis, nor malaria has anything to do with it. The children of the well-to-do are relatively more frequently attacked than those of the poor. It tends to run in families, child after child of the same parents succumbing within a year or two of birth. Mukerji remarked that the disease is especially apt to occur in grossly overfed and pampered children in Bengal, and has adduced evidence that the virus is probably conveyed by the mother's milk to the child. Green-Armytage believed the true ætiology to be a deficiency of vitamins in the mother's diet, thus depressing the mammary secretion and the endocrine system of the foetus, in overfeeding of the child when born, and insufficient feeding of milch animals. K. Rao, who isolated *Bact. coli* from the liver and ascitic fluid, believed that the essential factors are cow's milk and the toxins of *Bact. coli*. In favour of this hypothesis, he found that the substitution of modern infant milk foods for cow's milk prevents the occurrence of further cases in cirrhosis families. One critical instance is cited of mixed twins in which the female on cow's milk developed cirrhosis, whilst the breast-fed male escaped. Himsworth and Glynn (1944) have described two types of dietary cirrhosis; in the first the fibrosis is diffuse, following fatty infiltration and is caused by choline deficiency; in the second it is coarse, follows massive necrosis and is caused by deficiency of sulphur-amino-acids. There also appears to be some evidence that cirrhosis of the liver in childhood may be the sequel of fatty liver disease of malignant malnutrition or kwashiorkor.

Pathology.—Gibbons gave an elaborate and most careful account of the pathological anatomy of this disease; he concluded that it is a peculiar form of biliary cirrhosis, the consequence of the action on the liver-cells of some irritant of gastric origin, which leads to degeneration of the cells in the first instance, with subsequent increase of intercellular connective tissue and, later, of the portal sheaths. The formation of new bile-ducts between the hepatic cells, which is a

well-marked feature, he regarded as evidence of a natural curative effort, having for its object a regeneration of the liver-cells. Green-Armytage called the disease intercellular hepatic cirrhosis. R. Rao (1935) contributed the most profound study up to date by the application of the silver impregnation method. He concluded that the disease is a subacute *toxic* cirrhosis. On the other hand Krishna Rao thinks that it is similar to Lœnnec's or portal cirrhosis. He emphasizes the varying degrees of necrosis of the liver cells, the avascular œdematous connective-tissue network, and the obliterative lesions of the terminal and some of the bigger divisions of the hepatic venous tree without appreciable changes in the portal and biliary trees. There is also a poor attempt at regeneration of the hepatic parenchyma.

Studies by Khanolkar (1955) by liver biopsy reveal that the earliest changes consist of a widespread liver degeneration associated with a mild cellular reaction in Glisson's capsule. Condensation of the reticular fibres in the portal tract follows, with disruption of the *lamina limitans* and formation of pseudolobules. The fibrosis is entirely portal and eventually it extends so that wide areas of parenchyma become replaced by fibrous tissue. The process suggests a primary cellular degeneration leading to necrosis and which finally becomes irreversible and progressive. The evidence is in favour of an infective factor.

Symptoms.—Commencing insidiously, the characteristic initial enlargement of the liver may have made considerable progress before the disease is suspected. In the course of one or two months the liver has enlarged to the iliac crest. It is smooth and hard, and in some cases also, the spleen is hypertrophied. Nausea, occasional vomiting, sallowness, feverishness, constipation, anorexia, irritability of temper, thirst, and languor call attention to the child's condition. Fever of a low type sets in; the sallowness deepens into profound jaundice; the stools are clay-coloured; the urine is dark with bile, and there may be a terminal ascites, with puffiness of the feet and hands. (Fig. 77.) The skin may be bronzed almost as deeply as in Addison's disease. The veins become prominent on the abdominal wall. In five months from the onset, ascites and œdema of hands, feet and eyelids appear, and in the terminal stages (8–10 months) gastrointestinal hæmorrhages are found. Bile pigments, bile salts and albumin appear in the urine. Sooner or later, death from cholæmia ensues. Secondary infections are not uncommon. The leucocyte count varies from 14,000 to



Fig. 77.—Advanced case of cirrhosis of the liver with ascites and œdema of the hands and feet, but no jaundice. (After Krishna Rao.)

50,000 in the terminal stages, the increase being due to lymphocytes. The accompanying anæmia is microcytic.

Diagnosis.—For scientific diagnosis of various forms of tropical liver cirrhosis the method of aspiration liver biopsy should be introduced (Sherlock, 1946). In jaundiced patients vitamin K should be given for three days before the puncture is made (5 mgm. "Kapilon" by the mouth three times daily). With the patient lying supine with the right arm behind the head, a firm pillow should be placed under his left side to tilt his body slightly to the right. The cannula of the aspirator is 15 cm. long and 1 mm. in bore, is fitted with a handled trocar and a 20 ml. "record" syringe is used. The puncture is made in mid-axillary or anterior axillary line in the ninth or tenth intercostal space. The skin, pleura and liver capsule are infiltrated with 2 per cent. procaine. The trocar and cannula are passed through the skin and the patient instructed to take a deep breath to displace the lung upwards. The trocar and cannula are passed $\frac{1}{2}$ in. into the liver, the former is then withdrawn and the cannula pushed in a further 4–5 cm. to punch out a cylinder of liver tissue. The syringe is then attached and suction maintained whilst the cannula is withdrawn. The liver fragment is usually found in the barrel of the syringe. If there are any signs of hæmorrhage a blood transfusion must be given. Difficulties may arise in hepatic cirrhosis with much ascites. The risk of hæmorrhage is greatest in severely jaundiced patients. The information obtained from sections is reliable and sections of 10–20 liver lobules may be cut from the piece removed.

Treatment.—According to Green-Armytage, when cases are seen early and parents are given the necessary instruction, recovery takes place in six to ten weeks. Whenever possible, in a family in which several cases of this disease have already occurred, the latest baby should be immediately removed from the mother and artificially nursed and fed upon milk-foods such as Glaxo, Cow and Gate, Ostermilk and Nestlé's foods. Protein hydrolysate (casein hydrolysate) is given in doses of 2–4 teaspoonfuls daily; oranges and tomatoes supply vitamin C; small quantities of rice are well tolerated. Choline is administered in a mixture 15–20 gr. per dose three times daily.

Prophylaxis.—The mother must be fed properly in the antenatal and nursing periods. When weaning begins, the child should be fed on specially prepared infant foods, and 2–3 oz. of fresh fruit should be given daily; iodized salt (iodosol) should be added to all food, as vegetables in Bengal are deficient in salts.

CHAPTER XXXI

CHOLERA

Synonym.—Cholera Asiatica.

Definition.—Cholera (*Χοληροια* = flow of bile) is an acute, infectious, epidemic disease, characterized by profuse purging and vomiting of a colourless watery material, by muscular cramps, suppression of urine, algidity and collapse, the presence of the cholera vibrio in the intestines, and by a high mortality.

Geographical distribution.—It is probable that from remotest antiquity cholera has been endemic in Lower Bengal and in Central China, and has from time to time spread as an epidemic over India.

From a study of the march of epidemics it is to be concluded that cholera reaches Europe by three distinct routes—(1) *via* Afghanistan, Persia, the Caspian Sea, and the Volga valley; (2) *via* the Persian Gulf, Syria, Asia Minor, Turkey in Europe, and the Mediterranean; (3) *via* the Red Sea, Egypt, and the Mediterranean. Swaroop and Pollitzer (1954) have given an account of the world incidence since 1923 and define certain endemic foci in India and Burma which are related to the water systems near the coast at a low level and which are densely populated. It has not been possible to trace the manner in which the infection is maintained in them, or the method of infection from patient to patient, especially in inter-epidemic periods. There are other large areas in India which suffer from epidemics, but are often free in inter-epidemic periods and are therefore *not* epidemic zones.

Epidemiology and endemiology.—Cholera follows the great routes of human intercourse, and is conveyed chiefly by man—probably in its principal extensions by man alone—from place to place. In India, during religious gatherings, hundreds of thousands of human beings are collected together under highly insanitary conditions, as at the Hurdwar and Mecca pilgrimages (Fig. 78). Cholera breaks out among the devotees, who, when they separate, carry the disease along with them as they proceed towards their homes, infecting the people of places they pass through. The Hedjaz has, for the last 100 years, been the point of relay of cholera in its progress from the Far East towards the West. During that period there have been more than 27 outbreaks. In India cholera appears to spread from its home in Lower Bengal over the northern and western, central, and southern provinces in a series of waves of two to four years' duration. Cholera never travels faster than a man can travel; but in modern times, owing to the increased speed of locomotion and the increased amount of travel, epidemics advance more rapidly and pursue a more erratic course than they did eighty years ago. On the other hand, isolated countries, such as the Andaman Islands, Australia, New Zealand, the Pacific islands, the Cape Province, and the West Coast of Africa, have so far escaped. An epidemic of considerable virulence occurred in Celebes (Dutch East Indies) in 1938 and exhibited several peculiar features. Cholera broke out in Bengal in 1947 and in the autumn months an epidemic of considerable proportions raged in the Delta of Egypt. Centres of less importance are Burma and the Philippines.

Truly endemic cholera centres are found in Lower Bengal and in the Yangtse Valley, China. According to Taylor, an endemic area is :—

(a) one in which the total number of months with absence of cholera deaths does not exceed 80 in 92 years ;

(b) one in which a break of five or more months in cholera incidence does not take place.



Fig. 78.—Pilgrims bathing in the Ganges during the Kumbh Mela. These festivals are followed by cholera epidemics. (Courtesy of "Life Magazine." Copyright 1950, Time Inc.)

Rogers believed that the condition necessary for the spread of cholera in India is an absolute humidity of over 0.400, and that by watching the climatic conditions which influence the seasonal and annual incidence of cholera, increased or epidemic prevalence should usually be foreseen in time for steps to be taken to lessen its spread.

In endemic areas temperature and absolute humidity are the main determining factors. In Bengal, in January, when the absolute humidity is low and the temperature relatively so, cholera is at its lowest ebb. As the temperature rises, so does the cholera incidence until May or June when the monsoon sets in; then the humidity rises, but the temperature falls, though it shows a minor rise in October as the monsoon subsides. Wei, in applying the principles of forecasting epidemics in Shanghai, found that cholera tends to occur only when the absolute humidity exceeds

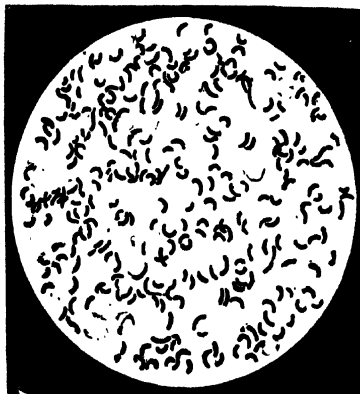


Fig. 79.—Cholera vibrio. Agar culture : 24 hours' growth. $\times 1,000$. (Muir and Ritchie.)

10 mgm. Hg. The combined study of periodicity of epidemics and humidity renders forecasting of epidemics possible.

D'Herelle made the interesting suggestion that the rise and fall of epidemics of cholera may be due to the amount of bacteriophage produced. Patients in whose stools no bacteriophage appears die of cholera. Those cases in whom bacteriophage is strong from the outset, rapidly recover.

Shell-fish have been suspected as a vehicle of cholera infection. This is especially likely in the clam, *Meretrix casta*, which is abundant in river estuaries on the E. Coast of India and is used extensively for food. Cholera occurs frequently in the fishermen who collect them. No evidence, however, has been obtained that multiplication of vibrios takes place within them.

Ætiology. *Discovery of the comma bacillus, or vibrio.*—The cholera vibrio was first discovered by Koch in Egypt in 1883; this he confirmed in Calcutta in 1884 by finding it in every case of the disease examined. His observations have since been abundantly confirmed. Rogers recounted that in India Surgeon-Major Macnamara suggested that cholera was due to living organisms spread by water many years before Koch.

Description of the cholera vibrio.—The comma bacillus (Fig. 79) is a very minute organism, 1.5 to $2\ \mu$ in length by 0.5 to $0.6\ \mu$ in diameter—about half the length and twice the thickness of the tubercle bacillus. It is generally

slightly curved like a comma; hence its name. After appropriate staining, flagella can be distinguished at each end or at one end only—sometimes one, sometimes (though less frequently) two. These flagella, though of considerable length—from one to five times that of the body of the bacillus—are difficult to see in ordinary preparations owing to their extreme tenuity. They are not always present during the entire life of the parasite. They impart very active spirillum-like movements. The individual bacilli, when stained, show darker parts at the ends or at the centre. Sometimes in cultures two or more bacilli are united, in which case an S-shaped body is the result; or several bacilli may be thus united, producing a spirillar appearance.

The comma bacillus is easily stained by watery solutions of fuchsin, or by Löffler's method, dried cover-glass films being used. It is decolourized by Gram.

The bacillus grows best in alkaline media at a temperature of from 30° to 40° C. Growth is arrested below 15° or above 42° C.; a temperature over 50° C. kills the vibrio. Meat broth, blood-serum, nutrient gelatin, and potato are all suitable culture media. It multiplies rapidly without curdling in milk; it dies rapidly in distilled water; it survives longer if salt be added to the water—for instance, 285 days in sea-water.

Culture by enrichment.—For the isolation of vibrios from stools the value of enrichment is recognized. The first method being inoculation into a weakly alkaline solution containing 1 per cent. peptone and 0·5 per cent. sodium chloride. Minor alterations in the medium were employed and high selective media such as Read's modification of Wilson and Blair's bismuth sulphide medium were evolved. A different method was introduced by Panja: Suspected cholera faeces are placed in a L_3 candle, fitted inside a test-tube containing peptone water to which boric acid has been added in concentration of 0·08 per cent. The vibrios grow through the candle after 24–48 hours' incubation. Potassium tellurite media have also been used with some success in suppressing the growth of coliform and other organisms. Dieudonné's alkaline blood-agar and a number of modifications, such as Kabeshima's, have been widely used in which hæmoglobin is employed instead of blood. A modification of Endo's medium, introduced by Aronson, is highly reliable. Bile-salt media, such as deoxycholate citrate-agar, are widely used.

In gelatin plates it grows readily as minute white colonies, irregular in shape, and granular, with surrounding liquefaction, into which the colonies of vibrios sink as into funnel-shaped depressions. Rough and smooth colonies are recognized. In gelatin stab-cultures the growth at first is most active near the surface; later, as growth proceeds along the needle track, a finger-shaped liquefaction results, which in time extends to the sides of the tube. In older cultures involution forms are common; they may die out after five or six weeks.

As a rule, the cholera vibrio does not produce hæmolysis, if blood be added to the medium such as agar, after twenty-four hours' incubation. The test is best performed in a fluid medium by adding varying amounts, from 1 ml. downwards, of a three days' culture in alkaline broth to 1 ml. of a 5 per cent. suspension of goat's corpuscles, and then thoroughly mixing. After incubation for two hours the tubes are placed in the ice-chest overnight and read the next day. With the solutions of sugars (1 per cent.) usually employed, the true cholera vibrio produces acid, without gas-formation, in glucose, mannite, saccharose, and maltose, but not from arabinose. Fermentation of lactose, with acid production, occurs two or three days later. The cholera-red reaction is obtained by the addition of pure sulphuric acid to a culture in 1 per cent. peptone solution. The peptone must be of a brand which contains tryptophane as this is necessary for the production of indole. Many other vibrios, such as *V. metchnikovi* give this reaction and also some water strains.

The true cholera vibrio belongs to Heiberg's Type I, and gives positive cholera red and negative Voges-Proskauer reactions; but does not produce early hæmolytic of erythrocytes. The former test is positive in El-Tor vibrios and other cholera-like organisms.

Certain organisms, known as the paracholera, or inagglutinable vibrios (Finkler-Prior and El-Tor), resemble the cholera vibrio minutely. Organisms found in fowl cholera, in decomposed cheese, and in river water also resemble it very closely, but, as they behave somewhat differently in the serological sense, they must be considered biologically distinct. Cultures of cholera vibrios have been swallowed many times by way of experiment, and, although in some instances diarrhoea has resulted, in only one case has true cholera been produced. Probably for the production of cholera several conditions are necessary, of which the comma bacillus is only one. Gastric acidity is an important factor in determining infection. When vibrios are ingested they are instantly killed in undiluted gastric juice. The difficulty of producing true cholera in lower animals by the administration of cholera cultures has exercised the minds of many, especially in the days following Koch's discovery, but more recently cholera-like symptoms have been produced in ground-squirrels by administering cultures of the organisms in alkaline media.

The preservation of *V. cholerae* in stools is based upon the favourable action of a suitable salt concentration along with its ability to survive at high alkalinity. Venkatraman and Ramakrishnan have devised a medium consisting of a boric acid buffer solution at pH 9.2 to which 2 per cent. salt was added. When a small quantity of cholera stool is added the vibrio can be recovered up to two months or longer.

Classification of vibrios.—Briefly stated, two main groups of vibrios are recognized:—

Group A.—Cholera and cholera-like vibrios.

Group B.—Other vibrios.

The vibrios in these two groups are morphologically similar, but biochemically and serologically distinct. Those of the latter group are less active fermentatively, but those of the former group are comparatively homogeneous. They have a common H antigen, but a number of O antigens which divide it into many sub-groups. It is recognized that the only fully reliable method for identification of the vibrio is the use of serological tests which will demonstrate the presence of the characteristic O-antigen of *V. cholerae*. Along with this, hæmolytic tests should be employed to eliminate the El Tor vibrios. The method is an agglutination test with a pure O high titre serum against a living or formalized suspension of the vibrio and not the use of an H and O serum against a boiled suspension. For the preparation of pure O sera, suspensions of *V. cholerae* are used of which the H antigen has been destroyed by prolonged boiling. Sera are raised with the antigen, usually in rabbits, by a series of doses over a short period. The sera prepared against O antigens of the Inaba and the Ogawa forms of the vibrio, will contain agglutinins, not only against the main antigen, but also against the subsidiary antigen, characteristic of the two forms. On the whole living suspensions of the vibrio are indicated. Formol suspensions are satisfactory. For preliminary diagnosis, rapid slide agglutinations with O sera diluted to 1 : 50 to 1 : 100 can be used, but these results should be confirmed by tube agglutination. Agglutination tubes should be placed in a water-bath at 52° C. and a preliminary reading made at the end of two hours. For the confirmation of rough, or partially rough, variants of *V. cholerae*, a high-titre serum prepared against a rough strain should be employed. Tests should be carried out with suspensions in 0.4 to 0.5 per cent. NaCl.

Bacteriophages.—About 13 races of bacteriophage which lyse the cholera vibrio have been isolated. They are known as A-N. Two of these only, A and N, are selective and act upon the true cholera vibrio only.

Isolation from water.—Taylor and Ahuja successfully isolated vibrios from water by collecting 200 ml. in screw-capped bottles to which 20 ml. of a solution of 10 per cent. peptone and 5 per cent. sodium chloride were added. The pH was raised to 9.0 with N/1 NaOH; thymol blue being the indicator. After incubation overnight 2 ml. amounts were added to 10 ml. quantities of peptone and after 6 hours' incubation one drop was placed on Aronson's medium. Several litres of water can be filtered through Kieselguhr-impregnated filter-paper. This is subsequently folded and placed in bismuth-sulphate enrichment medium and incubated.

Vibrios do not apparently produce any exotoxin. The *endotoxin* results from the destruction of vibrios within the bowel lumen. Burrows has shown that it is probably a phospholipid which can increase intestinal permeability without producing any detectable changes in the mucosa. Burnet and Stone have described a mucinase, a tissue-disintegrating substance, in cholera vibrio filtrates.

Methods of infection.—Infected material is conveyed from sick to healthy persons, either by water, food, flies or infected linen. Milk, raw fruit, such as dates in Egypt in 1947, vegetables and other uncooked foods are all able to serve as media for the transference of the vibrio. Clothing, if kept moist, can retain the infectivity for days and weeks. Greig has shown in India that, in stools kept in the dark at room temperatures, the average life of the vibrio is about eight days, but when dried, it only survives for a few hours. In water the vibrios remain viable for a considerable time. In reservoir water they live about two weeks, but some grossly contaminated streams, such as the Ganges, are unfavourable to their survival.

Cholera carriers.—Patients who have recovered from cholera may continue to excrete the vibrio irregularly for a few weeks, but, as a rule, 90 per cent. become free from infection in 14 days and 99 per cent. in a month. The existence of apparently healthy cholera carriers has been recognized, and these may excrete vibrios for two months, though the "carrier state," such as is known in typhoid, does not exist for cholera. Taylor definitely states that the convalescent and contact carriers in most cases are free from the vibrio five days from the onset of the attack or contact.

Immunity.—The guinea-pig or rabbit may easily be immunized against the cholera vibrio by repeated intraperitoneal injections of killed cultures. The serum thus obtained shows marked agglutinative properties in a high titre to cultures of the organism. Furthermore, this serum, when injected into a non-immune animal, has marked protective power against even four or five times the lethal dose. When this happens, active bacteriolysis takes place (Pfeiffer's reaction). The test is performed as follows:

A loopful of a young agar-culture of the vibrio is added to 1 ml. of bouillon containing 0.001 ml. of anti-cholera serum, and is injected into the peritoneal cavity of a young guinea-pig; by means of capillary tubes inserted into the peritoneum, the peritoneal fluid is examined microscopically every few minutes. If the original culture was a true cholera vibrio, the organisms break up into

globules; if not, no change takes place. The inoculation of animals by cholera cultures produces an immune serum which is remarkable for its high agglutinating power, the titre going as high as 1 in 12,000. For an agglutination test to prove that vibrios isolated from the stools are those of true cholera, a serum of a titre of 1 in 4,000 should be used.

The technique of hæmagglutination of the vibrio of cholera is described by Felsenfeld and colleagues (1955). The adsorbed antigens were tested against increasing dilutions of homologous sera after incubation at 36° C. for 1 hour and left standing for 1 hour at room temperature, which gave the best results when the slide method was used. One drop of each serum dilution and one drop of antigen were mixed on excavations on a slide and then rocked. Visual clumping appeared rapidly with homologous antigens and agglutination was complete in 15 minutes.

Pathology.—Rigor mortis occurs early and persists for a considerable time. Curious movements of the limbs may take place in consequence of post-mortem muscular contractions. On dissection, the most characteristic pathological appearances in cholera are those connected with the circulation and with the intestinal tract.

If death occurred during the algid stage, the surface presents a shrunken and livid appearance. All the tissues are abnormally dry. The muscles are dark and firm; sometimes one or more of them are ruptured—evidently from the violence of the cramps during life. The right side of the heart and the systemic veins are full of dark, thick, and imperfectly coagulated blood which tends to cling to the inner surface of the vessels. Fibrinous clots, extending into the vessels, may be found in the right heart. The lungs are usually anæmic, dry, and shrunken, occasionally congested and oedematous. The pulmonary arteries are distended with blood; the veins empty. The liver is generally loaded with blood; the gall-bladder full of bile; the spleen small. Like all the other serous cavities, the peritoneum contains no fluid, its surface being dry and sticky. The inner surface of the bowel has generally a diffuse rosy-red, occasionally, an injected appearance. It contains a larger or smaller amount of the characteristic rice-water material, occasionally blood. The mucous membrane of the stomach and intestine is generally pinkish from congestion, or there may be irregular arborescent patches of injection here and there throughout its extent.

On microscopical examination of the contents of the bowel during the acute stage of the disease the cholera vibrio, in most cases, may be demonstrated. Usually it is in great abundance, occasionally in almost pure culture in the upper part of the small intestine and duodenum, but it may be very scarce in the large gut. Sections of the intestine show the vibrio lying on and between the epithelial cells of villi and glands.

On the whole the vibrios are confined almost entirely to the gastro-intestinal canal, mainly to the lumen. The cholera endotoxins causes a superficial denudation of the epithelium and increases its permeability so that there is great out-pouring of water and electrolytes with loss of fluid from the tissues and blood. The tissue changes could possibly be explained by dehydration of the tissues and by hæmo-concentration and low blood-pressure, which results in temporary ischæmia.

De and his associates have paid special attention to the renal and suprarenal changes of those who have died in the stage of shock. The kidneys show patchy ischæmia of the cortex with medullary congestion, and there may also be necrosis of the cortical tubules. It is thought that cortical vasospasm is responsible for the complete cessation of urinary secretion. In a histo-chemical examination of the suprarenal glands it was concluded that depletion of the lipid material from the cortex may be associated with increased liberation of cortical hormones, so that the suprarenals play an active part in the symptomatology of cholera.

Symptoms.—Although cholera may declare itself within a few hours of exposure to infection, it may also do so at any time up to ten days. Three to six days may be set down as the usual incubation period. An attack of cholera commences in one of two ways: either it may supervene in the course of what appears to be an ordinary case of diarrhœa, or it may come on suddenly, without any well-marked prodromal stage. During cholera epidemics diarrhœa is unusually prevalent. It is a common observation that at such times an attack of simple diarrhœa may, after a day or two, assume the characters of true cholera. The preliminary looseness in such cases is known as premonitory diarrhœa or cholerine and is, in fact, a mild form of cholera. Besides diarrhœa, other prodromata, such as languor, depression of spirits and noises in the ears are sometimes noted.



Fig. 80.—Dehydration and collapse on the first day of cholera. Note the sunken orbits. (Dr. C. J. Hackett.)

Description of the average case.—When true cholera sets in, profuse watery stools, usually associated with griping pains, and at first faecal in character, pour, one after the other, from the patient. Quickly the stools lose their faecal character, becoming colourless or, rather, like thin rice-water containing small white flocculi in suspension. (Some would disagree with the similarity to rice-water and suggest that barley-water would be more accurate.) Enormous quantities—pints—of this material are generally passed. Presently, vomiting, also profuse, at first perhaps of food, but very soon of the same rice-water material, supervenes. Agonizing cramps attack the extremities and abdomen; the implicated muscles stand out like rigid bars, or are thrown into lumps from the violence of the contractions (due to depletion of chlorides and hypocalcæmia affecting the neuro-muscular junction). The patient may rapidly pass into a state of

collapse. In consequence principally of the loss of fluid by the diarrhoea and vomiting, the soft parts shrink, the cheeks fall in, the nose becomes pinched and thin, the eyes sunken, and the skin of the fingers shrivelled like a washerwoman's (Fig. 80). The surface of the body becomes cold, livid, and bedewed with a clammy sweat; the urine and bile are suppressed; respiration is rapid and shallow; the breath is cold, and the voice is sunk to a whisper. The pulse soon becomes thready, weak, and rapid, and then after coming and going and feebly fluttering, may disappear entirely. The surface temperature sinks several degrees below normal—to 93° or 94° F.; whilst that in the rectum may be several degrees above normal—101° to 105° F. The blood-pressure is low. The systolic may register 50 mm. of mercury, but is frequently unregistrable. The patient is now restless, tossing about uneasily, throwing his arms from side to side, feebly complaining of intense thirst and of a burning feeling in the chest, and racked with cramps. Although apathetic, the mind generally remains clear. In other instances the patient may wander or may pass into a comatose state.

This, the "algid stage" of cholera, may terminate in one of three ways—in death, in rapid convalescence, or in febrile reaction.

When death from collapse supervenes, it may do so at any time from two to thirty hours from the commencement of the seizure, usually in from ten to twelve. On the other hand, the gradual cessation of vomiting and purging, the re-appearance of the pulse at the wrist, the increase of blood pressure and the return of some warmth to the surface may herald convalescence. In such a case, after many hours' absence, secretion of urine returns, and in a few days the patient may be practically well again. Usually, however, a condition known as the "stage of reaction" gradually supervenes on the algid stage.

Anuria.—The first signs of anuria are congestion of the mucous membranes and conjunctivæ, malar flush, delirium, and gradual increase in depth and rate of respiration. Recovery is marked by the passage of a few ounces of turbid, highly coloured urine and this is followed by a "critical diuresis" resembling that seen in some cases of acute glomerulo-nephritis.

Renal failure in cholera has been compared to anuria following crush injuries. The blood urea is invariably raised and may reach 350 mgm. Anuria may persist for 50 hours, and the patient may yet recover. When the patient passes 2 pints of clear urine in 24 hours the danger of relapse has usually passed. According to Maegraith and the modern school of physiological thought the main factor is *renal anoxia*.

The importance of charting the amount of urine, hour by hour, day by day, in the reactionary stage of cholera cannot be over-emphasized. These data are essential if threatened anuria is to be successfully combated.

Reaction or cholera typhoid.—When the patient enters on this stage the surface of the body becomes warmer, the pulse returns, the face fills out, restlessness disappears, urine is secreted, and the motions diminish in number and amount, becoming bilious at the same time. Coincidentally with the subsidence of the more urgent symptoms of the algid stage and this general improvement in the appearance of the patient, a febrile condition of greater or less severity may develop. Minor degrees in this reaction

generally subside in a few hours ; but in more severe cases the febrile state becomes aggravated, and a condition in many respects closely resembling typhoid fever, "cholera typhoid," ensues.

Hyperpyrexia is an occasional, though rare, occurrence in cholera. In such cases the axillary temperature may rise to 107° F., the rectal temperature perhaps to 109° F. These cases also are almost invariably fatal.

In cholera there is a considerable variety in the character of the symptoms and in their severity, both in individual cases and in different epidemics. It is generally stated that the earlier cases are the more severe, those occurring towards the end of the epidemic being on the whole milder.

Ambulatory cases occur during all epidemics, characterized by diarrhoea and malaise merely.

Cholera sicca.—A very fatal type is known as "cholera sicca." In these cases, though there is no, or very little, diarrhoea or vomiting, collapse sets in so rapidly that the patient is quickly overpowered as by an overwhelming dose of some poison.

Eye changes in cholera.—Osmotic dehydration in cholera can bring about a lens opacity, which, in lesser degrees, is reversible, so far as the physical state of the water in the lens is involved.

Therefore cataract may develop suddenly in the stage of collapse and may have a similar osmotic basis to that of diabetes. In cholera loss of fluid from the bowel may lead to osmotic dilution of the body fluids, including the aqueous, and consequent inflow of water into the lens.

A very early ocular sign is blue discolouration of the skin of the eyelids. Retraction of the eyeball due to dehydration occurs so that the eyes are kept half open. Lacrymal secretions dry up, thus allowing the conjunctiva and cornea to become vulnerable, leading to conjunctivitis, ulceration of the cornea, keratomalacia and even, sometimes, massive sloughing of the cornea and sclera. Post-choleraic conjunctivitis often ensues.

Complications.—The common complications are persisting enteritis, diarrhoea, corneal ulcers, cholecystitis and abortion in pregnant women. Pneumonia is common in the colder countries, but rare in hot ones. Gangrene of the extremities, penis and scrotum, formerly observed, is seldom seen nowadays.

These changes disappear on rehydration.

Clinical pathology. *Loss of fluid and salts*.—The total loss of fluid may amount to as much as 5 litres in 24 hours. The salt content in the rice-water stage is about 0.5 to 1.0 per cent. There is considerable loss of alkaline bases in stools which disturbs the osmotic balance and leads to acidosis. The vomits are usually less in volume than the stools and in contrast they are acid and contain a lesser amount of salt.

Blood changes.—The loss of fluid may be more than 60 per cent. in fatal cases. In the acute stages of the disease the specific gravity nearly always varies between 1,060 and 1,068, rarely reaching as high as 1,072 in natives of India, in whom the normal figure is about 1,054. There is also hæmoconcentration with red cell counts of 6 million and over. Leucocytosis is constant in cholera, the counts being 20,000 per cmm. in some. The percentage of neutrophil leucocytes is increased to 80 per cent. or over, compared with the normal of 68 per cent., while the number of lymphocytes

is diminished. This increase is more than can be accounted for by the concentration of the blood. The *protein* content of the blood is increased in the acute stage of cholera as follows:

						AVERAGE	NORMAL
Protein nitrogen	1.538	928-1,376
Fibrin	94	32-64
Globulin	812	192-464
Albumin	652	544-1,072

Blood urea.—There is a definite rise of blood urea in all patients from the time of onset of the attack. The urea increases progressively, but falls fairly rapidly in patients during recovery. In the acute stage it varies from 28 mgm. to 125 mgm. per 100 ml. with an average of 62 mgm. (compared with the normal of 15-35 mgm.).

Circulatory failure.—The profound circulatory failure which is such a feature of cholera is not of cerebral, but of peripheral nature. The loss of body fluid is of course a factor, but the distribution of the blood plays a much more important role in the circulatory changes which occur. The arteries and capillaries are empty and the veins engorged in the splanchnic area. The effective circulatory volume of the blood is very much reduced. There is a fall in blood pressure as the result of loss in circulating fluid, the systolic pressure being often 70 mm. or lower on admission to hospital. In severe cases there is no measurable diastolic pressure. The circulation time is lengthened owing, partially, to the increased viscosity of the blood.

Renal failure.—The loss of body fluid as a consequence of the evacuations produces a quick diminution of the flow of urine which proceeds to complete anuria. In many cases this persists for 2-3 days, or even longer, and is not incompatible with recovery, although if unduly prolonged prognosis becomes unfavourable. If the stage of anuria is short a "critical diuresis" occurs on recovery. An important factor in the causation of anuria is considered to be that of lowered blood pressure which is insufficient to maintain glomerular filtration. In anuria there is probably a *shunting* of blood from the cortex to the medulla of the kidney and which deprives the cortical glomeruli of most of their circulation.

Uræmia.—This condition occurs mainly in patients admitted more than 48 hours after the onset of the disease and attacked with particular severity and in whom it is difficult to restore urinary secretion. According to Shorten, post-choleraic uræmia is really a misnomer. The condition is really a retention as shown by the diminished alkalinity, phosphate retention and peculiar type of dyspnœa.

Sequelæ are unusual. Recovery is generally complete. Occasionally there are minor sequelæ, such as anæmia, mental and physical debility, insomnia, a diphtheritic inflammation of the mucous membranes of the intestines, fauces and genitalia, nephritis, different forms of pulmonary inflammation, parotitis apt to end in abscess, ulceration of the corneæ, boils, bedsores, and gangrene of different parts of the body. Jaundice occurs at times, and is said to be of the gravest import. An interesting,

but unusual, sequel is bradycardia. Pregnant women almost invariably miscarry, the foetus showing evidences of cholera.

The prognosis of cholera is especially bad in opium addicts.

Diagnosis.—During the height of an epidemic the diagnosis of cholera is generally easy; the profuse rice-water discharges, the collapse, the cold clammy skin, the cyanosis, the shrunken features, shrivelled fingers and toes, the feeble husky voice, the cold breath, the cramps, and the suppression of urine, together with the high rate of mortality, are generally sufficiently distinctive. But in the first cases of some outbreaks of diarrhoea, which may or may not turn out to be cholera, and the true nature of which, for obvious reasons, it is important to determine, correct diagnosis may not be so easy. Control measures should be applied if the clinical evidence is suggestive, without waiting for bacteriological confirmation.

In the first place the stools should be examined microscopically. If vibrios are present in large numbers they may be detected by their scintillating rotatory movements in hanging-drop preparations, or by their characteristic shape in faecal films stained by carbolfuchsin. Diagnosis may be made:—(a) Inoculate several loopsful of stools into a tube of peptone water (1 per cent. peptone, 0·5 per cent. sodium chloride adjusted to pH 8·4). Incubate for eight hours. Take a loopful and examine fresh or stained for Gram-negative motile vibrios; (b) take a loopful from the peptone culture and streak on Vedder and Van Dam (hæmoglobin-peptone-glycerine and KOH—pH 8·4), Dieudonné, or Aronson plates for 12 hours. Pick out greenish in the first two, or red in the third, colonies and confirm that they are vibrios; (c) carry out agglutination tests with standard high-titre and anti-O sub-group 1 cholera serum to exclude all but El-Tor, and true cholera vibrios; (d) in order to show whether hæmolytic (El-Tor), or non-hæmolytic (true cholera vibrio), to a 5 per cent. sheep-blood corpuscular suspension in saline add an equal quantity of vibrio emulsion. Incubate at 37° C. and read after two hours and again after eight hours.

Bandi's method consists in inoculating the suspected faeces into peptone water containing agglutinating serum of such strength as to clump the cholera bacillus in high dilution. Within as short a period as three hours' incubation, agglutination visible to the naked eye is said to be present. This method, when employed in a large number of cases, necessarily consumes a large quantity of immune serum. According to Shousha in the Egyptian epidemic of 1947 diagnosis was greatly facilitated by taking swabs from the rectum.

In an autopsy on a suspected case of cholera at least two sections of the small gut, each about 5 in. in length—one just above the ileocaecal valve, the other in the middle of the ileum—should be ligatured, cut off, dropped into sterile saline and sent to a bacteriological laboratory as soon as possible for examination.

Taylor made it plain that the question of H and O agglutinins is important in the diagnosis of cholera, as it is in other intestinal diseases of bacterial origin. The H element is present in some strains of true cholera and also in all the saprophytic water vibrios. It is affirmed that the O agglutinin is all-important. Evidence is accumulating that the O groups of vibrios are responsible for most of the serious outbreaks of cholera. Therefore, it is important that sera from cholera cases should be tested for O agglutinins.

Differential diagnosis.—True cholera may have to be differentiated from mushroom poisoning, which may simulate it very closely, but in this instance there is usually a history of several persons having been

attacked at the same time. Leucocytosis is absent in food-poisoning though usually found during the early stages of cholera.

Differential diagnosis of cholera from food poisoning is based upon the violent and distressing vomiting which precedes the diarrhoea, the severity of the abdominal pain and the greenish offensive nature of the stools. The urinary flow is never suppressed, whilst the axillary temperature is raised.

Algid or choleraic subtertian malaria may simulate true cholera very closely (see p. 54); *acute bacillary dysentery* may occasionally be so sudden and severe in its onset as to resemble cholera; acute trichinosis is distinguished by leucocytosis and pronounced eosinophilia; in *arsenical or antimony poisoning* vomiting, continuous, mucous and often freely streaked with blood, is more usually the most urgent commencing symptom. Children suffering from cholera are apt to develop hyperpyrexia with cerebral manifestations, which may be mistaken for meningitis. Salient points of differential diagnosis are set out below:

TABLE VI

	CHOLERA	FOOD POISONING
<i>Diarrhoea.</i>	Often associated with griping. Precedes vomiting.	Associated with some intestinal pain. Follows vomiting.
<i>Vomiting.</i>	Causes no distress. Watery and projectile; follows diarrhoea.	Often violent and distressing. Vomit consists of food and is never watery. Copious or projectile. <i>Generally precedes diarrhoea.</i>
<i>Nausea.</i>	Absent.	Constant.
<i>Retching.</i>	Rare.	Constant, often severe.
<i>Abdominal pain.</i>	Not usually severe.	Constant.
<i>Tenesmus.</i>	Absent.	Common.
<i>Stools.</i>	Watery and copious.	Liquid, faecal, and offensive. Never colourless and copious.
<i>Urine.</i>	May be completely suppressed.	Never suppressed.
<i>Muscular cramps.</i>	Constant and severe.	In very severe cases confined to extremities.
<i>Collapse.</i>	Frequent. Chiefly from loss of fluid.	Faintness and syncope from toxæmia.
<i>Fever.</i>	Surface temperature below normal, but rectal temperature may be raised.	Axillary temperature 99–100° F.
<i>Headache.</i>	Absent.	Frequent.

TREATMENT

SPECIFIC TREATMENT.—Sulphaguanidine is tolerated in very large doses. That recommended is 0·1 gm. per kilo body-weight, immediately followed

by 0.05 grm. every four hours. That is to say that a patient of moderate size—50 kilos or 110 pounds—should receive an initial dose of 5 grm., followed by 2.5 grm. every four hours until symptoms subside. Formocibazol may be more effective than sulphaguanidine (Collier) (*see* p. 869).

Johar (1958) found that he obtained the best results by a mixture of dihydro-streptomycin, sulphadiazine, sulphamerazine and sulphamethazine. Chaudhuri, Das, Ghosal and others have undertaken extensive trials with various antibiotics such as chloramphenicol, oxytetracycline, and aureomycin, given by oral and intravenous routes. They found that though the stools are sterilized within 24 hours, the clinical results obtained proved inconclusive.

Kaolin, or “bolus alba,” as an adsorbent, has been disappointing. It consists of kaolin 200 grm. (7 oz.) in 400 ml. of water.

Subsidiary measures.—The patient should be kept strictly in the horizontal position, in a warm bed, and in a well-ventilated, but not too cold room. Thirst should be treated by sips of iced water, soda-water, champagne, or brandy and water. Copious draughts, as they are likely to provoke vomiting, are usually condemned. It does not follow from this that they are harmful; the emesis contributes to the elimination of toxins. Cramps may be relieved by gentle frictions with the hand, by a small hypodermic injection of morphia, or, these failing, by chloroform inhalations.

The surface heat is maintained by hot-water bottles or warmed bricks placed about the feet, legs, and flanks. The patient must not be allowed to get up to pass his stools; a warmed bed-pan should be provided for this purpose. The foot of the bed should be raised. All food should be withheld while the disease is active.

Maintenance of biochemical equilibrium.—These measures are: (1) Replacement of fluids; (2) Maintenance of blood and tissue chlorides at their natural levels; (3) The counteraction of acidosis.

Intravenous salines.—For the stage of collapse, which is due to the loss of a large amount of fluid, intravenous injections of salines must be resorted to in order to restore the balance. Collapse in cholera does not differ fundamentally from that due to hæmorrhage, and similar principles of treatment underlie both. Intravenous injection of normal saline is therefore indicated, but success appears to depend on the introduction of a sufficient quantity. Three to four pints may be necessary. The modern drip transfusion method should be used whenever possible.

When the pulse recovers and the patient complains of oppressive pain in the chest the rate of transfusion should be decreased and given at a rate of 1 pint in 15–20 minutes, but if the rectal temperature is 101° F. or above, all intravenous infusions should be given with caution or hyperpyrexia may occur.

A blood-pressure below 70 mm. of mercury indicates a dangerous collapse, and a specific gravity of the blood of 1063, or over, indicates a loss of half the fluid from the blood. In the acute stage the specific gravity of the blood varies between 1060 and 1072, the normal figure for a European adult being 1058 and for an Eastern native 1056.

The specific gravity of the blood is estimated by employing a series of small bottles of aqueous glycerin with specific gravities increasing by 2° per bottle

from 1048 to 1070. The specific gravity may be controlled by a urinometer. Blood from the patient is dropped on to the surface of the fluid in the bottles by a capillary pipette. The drop which remains stationary in the centre of the glycerin solution of a given strength indicates its specific gravity.

In the stage of collapse, anuria often occurs, and every effort must be maintained to re-establish the blood-pressure. Pituitary extract, or pitressin, is often useful during the stage of reaction, given in doses of $\frac{1}{2}$ to 1 ml., hypodermically, two to four times a day. Caffeine citrate, 5 gr., is useful as a cardiac tonic and as a diuretic; it may be given three or four times during the twenty-four hours. Chatterjee (1953) finds that avomine, 25 mgm. (promethazine and 8-chlorotheophyllene), 1-2 tablets, checks the intractable vomiting and so permits the oral replacement of fluid.

Mortality-rate.—The death-rate for cholera has always been high. In former days in India it was seldom less than 70 per cent. In the decade ending 1908 it was 54.2 per cent. in Indian and 78.5 per cent. in British troops in India. With improved methods of treatment it has declined, but is still about 20 to 30 per cent. The death rate in collapsed cases is considerably higher, and, even with modern methods, remains about 65 per cent. Under hospital conditions at present it is about 10 per cent. In epidemics it is usually found that the death rate is higher at the beginning than at the end of the epidemic.

The prognosis is unfavourable in those over fifty years of age and in children under five.

Prophylaxis. *Quarantine prevention.*—Theoretically, quarantine should be an efficient protection against the introduction of cholera into a community. Even if the utmost care, intelligence, and honesty succeed in excluding individuals actually suffering from cholera, or likely within a reasonable time to suffer from it, there is yet no guarantee that the germ of the disease may not be introduced. Convalescent patients may pass vibrios in their stools. For the recognition of the carrier state it is necessary to examine the stools of all contacts.

Attention is being given to sanitation rather than to quarantine. During the great religious festivals the sanitary condition of the devotees is looked after as far as practicable, special care being given to provide them with good drinking and bathing water. On the appearance of cholera in the vicinity of troops in India, special protective measures were promptly instituted, elaborate directions having been drawn up for the guidance of medical officers.

Potassium permanganate is the popular disinfectant for wells. The main advantage lies in its extreme simplicity of application. Its action on cholera vibrios in high dilution appears specific, but the customary criterion of adding permanganate until the water is slightly pink is unsafe. A dilution of 1 : 500,000, which produces a faint purple colour in filtered water, kills cholera vibrios in a short time. This dilution is obtained by adding $\frac{1}{2}$ gr. of permanganate to each gallon of water, or roughly 1 lb. to each 50,000 gallons. In a well of 1,768 gallons the amount would be $\frac{1}{2}$ oz. Neither permanganate nor bleaching powder should be thrown into the well, but the

mixture should be made in a bucket, the supernatant fluid should be poured off until the whole amount has gone into solution, then it should be mixed thoroughly with the well water by repeatedly lowering and raising the bucket.

General disinfection of water supplies.—For chlorination the usual rule is 1 part in 5 million (chlorine content in bleaching powder is $83\frac{1}{2}$ per cent.), or 6 lb. of bleaching powder per million gallons of water.

Haffkine's inoculation.—During the 1914–1918 war many millions of anticholeraic inoculations were made. The initial dose is $\frac{1}{2}$ ml. of an emulsion of 4,000 millions, followed seven to ten days later by a second inoculation of 1 ml. containing 8,000 millions. Experience has shown that even larger doses can easily be tolerated. Local reaction is, generally speaking, very mild. There may be œdema and a painful infiltration at the site of the injection, rarely followed by systemic disturbance.

Several strains of cholera vibrios are used. They are inoculated into Roux bottles containing "pea-extract agar" and grown for forty-eight hours. The growth is washed off with normal saline, and the emulsion counted, with dark ground illumination. The emulsion is then heated to 55° C. for one hour, after which 1 per cent. carbolic is added. The emulsion, thus sterilized, is finally diluted down so as to contain 8,000 million vibrios per ml. of saline and 0.5 per cent. carbolic.

The immunity thus produced does not seem to be very persistent, lasting at the maximum for three or four months.

Experience, particularly that obtained during the Balkan War in 1913, in Batavia in 1915 and 1916, and in the 1914–18 war, has gone far to confirm the earlier impressions of the value of Haffkine's inoculation.

In India from 1905–1916 the annual number of deaths attributed to cholera was never less than 300,000. Epidemics of cholera are readily controlled by vaccine when inoculation is made compulsory; thus, when this disease was introduced into Korea from China in 1926, the outbreak was promptly brought to a close by the inoculation of more than one million persons.

The outbreaks of cholera in Egypt in 1947 offered an opportunity of estimating prophylactic value of cholera vaccine. It was shown that villages, in which inoculation was carried out before cases of cholera had occurred, showed a lower incidence and case mortality than those in which inoculation was commenced after the outbreak.

Rogers has long advocated compulsory inoculation for the control of cholera in pilgrims in India and has quoted figures in relation to this measure since 1940. There has been an unprecedented and rapid decline of cholera mortality amongst 20 million pilgrims. During 15 years—1941–1955—about 300 million people have been inoculated in India. Formerly the pilgrims became infected and carried back the disease to their villages. There are areas where cholera is endemic at all seasons of the year, because of the monthly absolute humidity, such as Burma, Siam and Indo-China, which are contiguous with endemic areas of Assam and the eastern provinces of Greater Bengal, from which cholera epidemics spread over north-west and central India. To strike at the root of the problem it is essential that the endemic regions of Burma, Siam, and Indo-China should adopt the successful Indian plan of enforcing compulsory inoculation, every year, of all pilgrims within their territories (Rogers, 1958).

CHAPTER XXXII

THE DYSENTERIES AND LIVER ABSCESS

THREE types of dysentery, correlated to three specific and, zoologically, widely separated parasites, have now been definitely established. Though of a totally distinct ætiology they are not mutually exclusive, for one type may be superimposed upon or complicate another; moreover, any, or all of them, may be implanted on some general disease, such as malaria or typhoid. The term "dysentery" denotes a symptom-complex, but does not indicate any particular disease of distinct ætiology. It is most important that a sane and critical view should be taken on this differential diagnosis of the dysenteries as there are many pathological conditions of the intestines which may give rise to a discharge of blood and mucus, but which are unconnected with any parasitic infection.

The principal forms of dysentery and their respective parasites are as follows :

I. BACTERIAL—

THE BACILLARY DYSENTERIES :

Shigella dysenteriae—Schmitz, Flexner, Newcastle and Sonne bacilli.

II. PROTOZOAL—

AMÆBIASIS—Amœbic dysentery, Liver abscess, etc.

Entamoeba histolytica.

BALANTIDIAL DYSENTERY :

Balantidium coli.

III. HELMINTHIC—

BILHARZIAL DYSENTERY :

Schistosoma (Bilharzia) mansoni, *S. hæmatobium*, *S. japonicum*.

VERMINOUS DYSENTERY :

Esofphagostomum apiostomum and *E. stephanostomum*.

I. BACILLARY OR EPIDEMIC DYSENTERIES

EKIRI—Japanese

Definition.—Acute epidemic diseases due to invasion of the mucosa of the large intestine by specific bacilli (*Sh. dysenteriae*, Schmitz, Flexner, Newcastle or Sonne). Pyrexia, symptoms of toxic absorption, and the discharge of blood-stained mucus in the stool usually occur. In severe cases coagulation necrosis of the mucosa may take place and quickly lead to death. In the milder forms the clinical symptom may be a simple diarrhoea.

Geographical distribution.—Epidemics of bacillary dysentery are frequent, both in the tropics and in temperate countries. At present such epidemics are of greater intensity and frequency in those countries in which insanitary habits and more primitive conditions lend themselves to the spread of disease. In mediæval times bacillary dysentery epidemics seem to have been much more widespread and virulent at a time when the sanitary conditions were more akin to those now prevailing among primitive tropical natives. In Europe, bacillary dysentery is mainly an institutional disease, occurring not infrequently in lunatic asylums, prison camps, and military barracks. In the Gallipoli campaign (1915) it was responsible for the majority of the 120,000 medical casualties evacuated at that time. Sonne dysentery has been widespread, especially in children, during recent years, in winter time, in England, Europe and America.

Epidemiology.—In the tropics and subtropics bacillary dysenteries appear to observe a definite seasonal incidence. They are certainly prevalent during the rainy season and for a short subsequent period, but mostly in the autumn months, whilst minor epidemics may also occur in the early spring. During the hot dry African summer they are in abeyance. Epidemic dysentery is associated with the rainy season in the tropics for the following reasons:—The rains deter people from defæcating at a safe distance from the village; waterlogging of the soil prevents the bacilli from dying out; people are more liable to chills, which often cause an acute attack; natives crowd together, a tendency which increases the chances of infection, together with increased risk of pollution of water supplies. The infection, as a rule, spreads rapidly from man to man.

Bacillary dysentery has always been a scourge of war. During the 1939–45 world war, though bacillary dysentery was prevalent in the earlier stages in the Middle East, yet it was milder in type and eventually, owing to successful treatment with sulphaguanidine, it became unimportant.

Indirect contagion. (a) *Flies*.—There appears to be little doubt that houseflies (*Musca domestica*) commonly act as carriers of the infection. The seasonal incidence of bacillary dysentery corresponds in a remarkable manner with the maximum prevalence of these pests. The housefly is able to spread dysenteric infection, firstly by regurgitation preparatory to feeding on food; and secondly (probably more commonly) by its fæces. This was first found by the Editor in Fiji in 1910, and afterwards in the Sinai desert in 1917. There was no doubt that in Gallipoli the swarming houseflies were the main factor in the epidemic. This work was confirmed by Stewart (1944) who found, in North Africa, that houseflies could carry virulent dysentery bacilli for as long as 11–12 days.

(b) *Water* acts as a medium of infection, especially in Indonesia and Malay States. It has been shown that the bacillus can survive in drinking-water for over three weeks, but not for long when exposed to the sun, or when associated with putrefactive micro-organisms.

(c) *Milk*.—Several outbreaks of Flexner and Sonne dysentery in southern England and in Europe have been ascribed to contaminated milk.

TABLE VII.—BIOLOGICAL REACTIONS OF PATHOGENIC AND ALLIED ORGANISMS RECOVERED FROM THE FÆCES

	Mannite	Glucose		Maltose		Lactose		Saccharose		Dulcite	Litmus or Phenol Red Milk			Indole	Motility
	A	G	A	G	A	G	A	G	A	G	A	Alk	Clot		
<i>Shigella shigæ</i> . . .	0	0	+	0	0	0	0	0	0	0	0	+	0	0	0
<i>Shigella flexneri</i> . . .	+	0	+	0	+	0	0	0	0	0	0	+	+	0	0
<i>Shigella schmitzi</i> (<i>S. ambigua</i>) . . .	0	0	+	0	0	0	0	0	0	0	0	+sl.	0	0	0
<i>Shigella sonnei</i> . . .	+	0	+	0	0	+	0	+	0	0	0	+	0	+	0
<i>Shigella newcastle</i> . . .	±	0	+	+sl	+	—	—	—	—	—	+	+	+sl later	—	+
<i>Salmonella morganii</i> . . .	0	0	+	+sl	0	0	0	0	0	0	0	0	+	0	+
<i>Salmonella typhi</i> . . .	+	0	+	0	+	0	0	0	0	0	0	+	0	0	+
<i>Salmonella paratyphi</i> A. . .	+	+	+	+	+	+	0	0	0	0	+	+	0	0	+
* { <i>Salmonella paratyphi</i> B. * <i>Salmonella enteritidis</i> . . .	+	+	+	+	+	+	0	0	0	0	+	+	+	0	+
<i>Bacterium coli</i> . . .	+	+	+	+	+	+	0	0	0	0	+	+sl	+	0	+
<i>Bact. acidii lactici</i> (Hügge) . . .	+	+	+	+	+	+	+	+	0	0	+	+	0	+	+
<i>Bact. allaliigenes</i> . . .	0	0	0	0	0	0	0	0	0	0	0	+	0	+	+

A = acid, G = gas, Alk = alkaline, Sl = slight.
 * To differentiate *S. enteritidis* and other organisms of the food-poisoning group from *S. paratyphi* B. serological tests must be applied.

(d) *Food*.—Sonne dysentery is a food infection and should be classified among the group of food-poisonings. One of the largest outbreaks in London in 1938 was ascribed to eating "pease pudding."

(e) *Susceptibility of the individual*.—New arrivals in the tropics are liable to this form of dysentery, and small children are specially so. Patients whose resistance has been undermined by intercurrent disease, such as malaria, pellagra and tuberculosis, are apt to suffer severely from terminal bacillary dysentery.

(f) *Carriers* (see p. 455).

Ætiology.—*Shigella dysenteriae* was discovered by Shiga in 1898, confirmed two years later by Kruse in Germany. It has therefore been known on the Continent as the Shiga-Kruse bacillus.

Shiga's bacillus is a rod-shaped Gram-negative organism, 1 to 3 μ in length | 0.4 μ in breadth; it is non-motile, and often exhibits very active Brownian movement. Vedder and Duval have demonstrated numerous lateral flagella of great tenuity. On agar and gelatin it grows as a thin smooth film with regular margins, and on MacConkey plates its colonies much resemble those of the typhoid bacillus; they are regularly round, light-blue and dew-like. It produces no liquefaction of gelatin, and grows as a transparent, almost invisible, layer on potato. With solutions of the sugars (see Table VII, p. 447) it produces acidity in glucose, but is inert in the rest of the series and does not produce indol in peptone water. The organism may be agglutinated in high dilutions by the serum of patients suffering from the disease. It occurs in considerable numbers in dysenteric lesions, and in the blood and mucous stools in the early stages.

A variety of Shiga's bacillus (resembling that organism in its sugar reaction, but forming indol and not agglutinating with Shiga-immune serum) is known as Schmitz's bacillus and has been shown to be of considerable importance in the Middle East. (This organism is identical with *B. ambiguum* of Andrewes.)

Para-Schmitz organisms allied to, but antigenically distinct, form small discrete, smooth colonies on MacConkey's agar.

Cultures of *Sh. shigae* are toxic to laboratory animals, especially rabbits, but in these animals they do not produce lesions characteristic of dysentery, though filtered toxins, when injected intravenously, cause necrosis of the mucosa of the large intestine. In two experiments in man, one intentional, the other accidental, ingestion of pure cultures was followed, within a short time, by well-marked symptoms of dysentery.

Sh. flexneri (the Flexner-Boyd group).—In 1900 an organism morphologically similar to Shiga's bacillus, but differing in the production of acid from mannite as well as glucose, producing indol from peptone somewhat irregularly, and inagglutinable with Shiga-immune serums, was isolated by Flexner from cases of dysentery in Manila. From the work of Andrewes and Inman on a very large number of strains of Flexner—the mannite-fermenting group—it can be definitely stated that the organism does not adhere to one constant type, as does *Sh. shigae*, but differs greatly in the toxicity of the various strains and in their antigenic properties. Boyd (1938) in a study of antigenic variation among mannite-fermenting dysentery bacilli suggested that loss in culture of type-specific antigen, which is not shared by other members of the group, is associated with an increase, real or apparent, of non-specific group antigen. It seems probable that available cultures of the historical Hiss and Russell Y are degenerate variants of an original W strain, and that an Indian strain, 103A, is the type-specific

Flexner-Y. This has been found to be fairly common, both in the United Kingdom and in other parts of the world (W. M. Scott, quoted by Boyd). This work emphasizes the great importance of using type-specific suspensions in diagnostic agglutination tests. Stock Flexner-Y strains may on these grounds be almost or quite devoid of type-specific antigen.

The Newcastle bacillus, first recognized as a cause of dysentery by Clayton and Warren, corresponds to Boyd's No. 88 (see Table VII). It has now been found in parts of England, India and Nigeria. Owing to the fact that it forms small quantities of gas in solution of the sugars and is motile on first isolation, it frequently escapes detection.

Sonne's bacillus (*Shigella sonnei*), which ferments lactose slowly, is responsible for outbreaks of enterocolitis in Egypt and elsewhere, and may produce symptoms of food poisoning resembling those of the *Salmonella* group. The importance of this infection has been recognized in England and in America during recent years as a cause of dysentery and diarrhoea of definite seasonal occurrence, especially in children. The colonies of this bacillus tend to assume a much more crenated outline than do those of the Flexner type, but are usually larger than those of Shiga or Flexner on MacConkey's medium. Cultures of *Sh. sonnei* are not agglutinated by standard Flexner or Shiga sera. When titrated against a specially prepared Sonne anti-serum, agglutination to full titre occurs. Often, however, when freshly isolated, the bacillary emulsion is inagglutinable, but will abstract the agglutinins from Sonne serum by absorption. On MacConkey's medium, Sonne colonies frequently show a small central point of acidity on a somewhat opaque background. This bacillus is indol-negative and xylose-negative. It ferments glucose and mannite in twenty-four hours, and lactose and saccharose after some days. Serological varieties and strains are now recognized.

Dysentery bacilli can be isolated from the intestinal canal and the mesenteric glands, and have also been obtained from the blood-stream, gall-bladder and joint-effusions. Selective cultivation media, especially for Flexner and Sonne bacilli, have been introduced and of these the best is Leifson's desoxycholate-citrate medium (Haynes' modification).

Toxins.—The O forms of *Sh. shigæ* contain both exo- and endotoxins. The former is insoluble in dilute trichloroacetic acid, whilst the endotoxin can be precipitated from watery solution by means of alcohol or acetone, after removal of the acid by dialysis, yielding 10 per cent. of dry weight of the organisms.

Pathology.—The primary lesions of bacillary dysentery (Shiga and Flexner infections) are confined to the solitary follicles of the large intestine, and result in a sinuous "snail-track" ulceration of the folds of mucous membrane. In very acute cases the process consists of intense hyperæmia of the large intestine, which eventually culminates in necrosis of the mucosa of the entire colon, as well as of the last 2-3 ft. of the ileum. Exceptionally, the whole extent of the mucosa of the small bowel may be involved.

As a general rule, the lesions characteristic of bacillary dysentery are most pronounced in the lower part of the intestinal canal, from the sigmoid flexure to the anus. In the stage of *necrosis* the large gut is contracted so as to resemble a stiff tube, whilst the mucous membrane is converted into a rigid, olive-green or blackish substance (Plate X, Fig. 3). This colour is thought to be due to the staining of the dead tissue by bile-pigments. Occasionally, the necrosis may have a patchy distribution affecting especially the descending and pelvic portions. There are many signs of profound toxæmia.

When the necrotic patches have a more local distribution, irregular ulcers, often communicating with one another by submucous sinuses, form and may

involve the entire wall, producing a fenestrated appearance. Inflammatory changes are found in the mesenteric glands, with macrophage activity.

In mild Flexner, Sonne and Schmitz infections the mucous membrane is red and inflamed, and in places there may be small abrasions or even shallow ulcers.

Chronic ulceration of the large gut may occur in bacillary dysentery. The smallest lesions are lenticular, involving the mucous surface. For the differentiation of these lesions from those of amoebic dysentery the reader is referred to Table VIII, p. 458. They should be distinguished from those of tuberculous, typhoid, schistosomal origin, or of ulcerative colitis.

Mucous retention cysts, due to the formation of pseudo-adenomata from the base of Lieberkühn's follicles, may sometimes be found as a sequel of ulceration. They may be recognized as jelly-like elevations forcing up the mucous surface, scattered throughout the length of the large gut. Dysentery bacilli may be isolated from their contents, and they are found in the large intestine of "carriers" of bacillary dysentery (Fletcher and Jepps) and undoubtedly represent the cause of this condition.

Many cases of chronic bacillary dysentery exhibit a granular condition of the mucous membrane of the large gut. The kidneys in Shiga infections may show patchy glomerular congestion and catarrhal changes. In cases of longer duration they are enlarged and the convoluted tubules necrosed, with extensive cloudy swelling. Nephritis is often the cause of death (Dick, 1942). Emboli in liver and spleen frequently occur.

Histopathology.—The submucosa is the seat of numerous hæmorrhages and of round cell-infiltration (Fig. 81). The ganglion cells of Auerbach's plexus are involved in perilymphatic inflammation. The formation of macrophage cells from the capillary endothelium of the vessels may also be observed. Owing to their large size, hyaline appearance, and vacuolated protoplasm, these cells are apt to be mistaken for *Entamoeba histolytica* (Plates XII and XIII). These cells appear in an early stage in acute ulcers and in the granulation tissue of chronic lesions.

The pathological appearances of Sonne dysentery are not so extensive as are those of Shiga and Flexner infections. The changes are, on the whole, similar, but not by any means so severe (Plate X, Fig. 2).

Symptoms.—After a short incubation period, usually of from one to seven days (as ascertained by experiment), the disease commences in a variety of ways, suddenly or insidiously, in all degrees of severity from mild diarrhoea to acute fulminating attack.

The main clinical symptoms are those of inflammation of the large intestine, viz., griping, tenesmus, frequent passage of loose, scanty, mucosanguineous stools, often with dysuria.

The onset may be attended by high or moderate fever, or there may be no rise of temperature. Vomiting may occur from the outset, or be absent altogether.

Palpation of the abdomen is difficult during the early stages, owing to the rigidity of the recti muscles. Later, especially in toxic cases, the abdomen may become quite lax, and the spastic sigmoid colon can be sensed as an elastic cord. Implication of other portions of the large intestine can usually be detected from tenderness on pressure.

Blood changes.—There are few characteristic blood changes. As a rule, there is a polymorphonuclear leucocytosis of 16,000–30,000 at the commencement of the attack, falling to normal or subnormal on the third or fourth day.

Character of the stools.—At first fæcal and diarrhœic, the evacuations may vary enormously in number and character. Their number may be uncountable, with the unfortunate victim “glued to the commode.” At first they consist of viscid blood-stained mucus, which bears some resemblance to “red-currant jelly” or “frog’s spawn.” They are



Fig. 81.—Microscopical section of large intestine in bacillary dysentery, showing necrosis of mucosa, cellular infiltration, and hæmorrhages into submucosa.
(P.H.M.-B. 1912)

generally odourless. The characters by which they may be distinguished from amœbic stools are given on p. 458. A few teaspoonsful may be passed. Subsequently they contain less blood and become more purulent. Finally, biliary pigments re-appear and fæcal characters may be re-established.

In the most acute and fulminating forms the mucus may be mingled with a large amount of altered blood and the evacuations come to resemble “meat washings.”

On clinical grounds, bacillary dysentery may be classified as follows :

1. *Mild or catarrhal bacillary dysentery.*—A common history is that for some days the patient had suffered from what was supposed to be an attack of diarrhoea. The stools, at first bilious and watery, perhaps four or five in the twenty-four hours, latterly and by degrees became less copious and more frequent, less fæculent and more mucoid, their passage being attended by some straining and griping.

At the same time the tongue may remain clean, and there may be no accompanying pyrexia. The attack may be over in a week, and the stools may number about twelve in the twenty-four hours. The majority of these mild cases are caused by Flexner, Schmitz, Newcastle or Sonne bacilli.

2. *Acute bacillary dysentery.*—In others the onset is much more abrupt. Within a few hours dysentery may be in full swing. The stools, at first fæculent, soon consist of little save blood-stained mucus. Very shortly the desire to stool becomes increased, the griping and tenesmus being accompanied, perhaps, by distressing dysuria. Fever, which at the outset may have been smart and preceded by rigor, subsides. The face is anxious

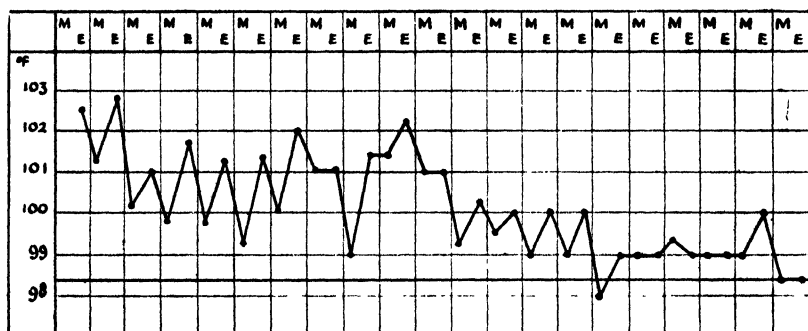


Chart 22.—Bacillary dysentery.

and pinched; the cheeks are high-coloured from a toxic flush. Slight delirium and mental confusion may be added to the clinical picture. Thirst may be considerable, anorexia complete, and the tongue white or yellow-coated. In a week or more the urgency of the symptoms may diminish, and the attack tapers off into a subacute or chronic condition, or it may end as abruptly as it began (Chart 22).

3. *Fulminating bacillary dysentery.*—These are invariably Shiga infections. The attack generally begins suddenly with chills or smart rigor, vomiting, headache, and a rapid rise of temperature to 100° or even 104° F. Very shortly after the rigor, purging begins, the stools rapidly assuming dysenteric characters. In from two to three days up to a week or longer, peripheral vascular failure sets in with a subnormal temperature, and the patient dies. The tongue is thickly coated. The abdomen is sunken and acutely tender. The stools rapidly become liquid, offensive, and greenish or greyish.

A *choleraic* form, in some respects resembling cholera, has been recorded. The onset is acute, with vomiting.

4. *Relapsing bacillary dysentery*.—In a proportion of bacillary dysenteries, although the urgency of the initial attack may subside, dysenteric symptoms do not completely disappear.

5. *Chronic bacillary dysentery*.—In a large proportion of cases of acute dysentery the faeces do not become absolutely normal for a considerable time after abatement of the more urgent symptoms. On the slightest indiscretion the symptoms re-appear provoking unexpected attacks of diarrhoea. For months, or even years, some patients never pass a perfectly healthy stool, the unformed stools always containing muco-pus or at times blood.

6. *Granular rectitis*, a granular excoriation of the last three inches of the rectal canal, with the passage of blood and mucus, persists as a not-uncommon sequel, especially in Shiga infections. This condition closely resembles idiopathic granular proctitis, which is usually harmless. In the former, as described by Cropper (1955), there is complete loss of the normal satin sheen of the mucosa and its place is taken by a coarse roughening of the surface due to exposure of the deeper layers.

Bacillary dysentery in children.—Infection with dysentery bacilli (Shiga or Flexner) in small children, especially in Europeans, may produce most acute and rapidly fatal symptoms. They may expire in convulsions before the intestinal symptoms have had time to develop. Cases may resemble meningismus, and at their onset, on account of the pyrexia and toxæmia, simulate enteric infections.

Post-dysenteric ascites.—This ascites, according to Snapper, may be associated with liver cirrhosis. Massive serous intraperitoneal effusions, many of which proved fatal, were recorded from the Middle East in 1941–1942.

Symptoms of Sonne dysentery.—In most cases mild attacks of dysenteriform diarrhoea are the rule. The faeces are greenish, or yellowish and offensive, with blood-flecked mucus from which the organism may be cultured. In the more acute attacks the symptoms more closely resemble those of Flexner dysentery, with sudden onset of colic, diarrhoea and, later, blood and mucus. Sometimes, however, they are still more acute, with pyrexia and vomiting. They may assume an alarming aspect reminiscent of salmonella infections. Then "tomato soup" stools are passed, followed by rapid prostration. Sonne infections are usually pyrexial at the time of the abrupt onset, but in the milder cases the fever is slight and transient. A feature is associated catarrh of the respiratory tract with diarrhoea. Acute Sonne infections, in children up to nine years of age, may cause sudden death. In mental institutions, especially, Sonne infections are apt to attack the inmates.

Cruikshank and Swyer found that, by repeated examination of faecal specimens and rectal swabs, Sonne's bacillus could be isolated with certainty in most cases, but that the latter method gave a higher proportion of positive results.

Complications.—*Dysenteric arthritis*, or *dysenteric rheumatism* was formerly fairly common. Effusions into the cavity and ligaments surrounding the joints, especially the knee and ankle, may take place during the acute stage, or, more generally, during convalescence when the stools are fæculent (Fig. 82). It may occur in some Shiga epidemics. Pyrexia is usually present. Exceptionally, permanent disability with development of osteoarthritis many years later may result. According to Graham,



Fig. 82.—Arthritis of hands and knees in bacillary dysentery.
(Dr. G. Hall).

complete recovery usually ensues, even after the arthritis has persisted for six months. Aspirated synovial fluid is sterile, but may agglutinate dysentery bacilli (Klein) in a titre considerably higher than that given by blood-serum. Shiga's bacillus has been isolated from the fluid in one instance (Elworthy).

Eye complications.—*Acute conjunctivitis* and *iridocyclitis* are now regarded as symptomatic of a dysenteric toxæmia. The former is frequently seen in association with arthritis, whilst iritis supervenes in a small percentage of cases. The pupils are irregular in outline, with ring synechiæ.

There is also anterior uveitis, with adhesions to the capsule of the lens, formed by a thin exudate occupying the pupillary space, causing photophobia, blepharospasm and marked circumcorneal hyperæmia. The aqueous humour has been found to agglutinate *Sh. shigæ*, though the tears do not contain specific agglutinins.

Other complications.—Parotitis, unilateral or bilateral, has been often observed. Intussusception of the small intestine has been found in children, and in acute cases may cause death.

During the recent 1939–1945 war the list of complications has been amplified to include intestinal hæmorrhage, perforation with peritonitis, chronic peritonitis with localized, or general, effusions of peritoneal fluid, pneumoperitoneum, portal pyæmia with multiple liver abscesses, thrombosed piles, rectal prolapse, peripheral circulatory failure in toxic cases, glomerulo-nephritis and renal failure in Shiga infections, pneumonia, and diffuse purpuric rashes. A non-specific urethritis is now also recognised.

Sequelæ.—Stenosis of the large intestine may result from acute attacks. Pain and abdominal discomfort may indicate formation of abdominal adhesions which are an occasional sequel. Rarely, megacolon may be produced. *Peripheral neuritis* of the legs may follow bacillary dysentery. *Post-dysenteric tachycardia*, or effort syndrome, a condition of irritable heart, may persist long after dysenteric symptoms have disappeared. *Achlorhydria*, rarely *achylia gastrica*, may be responsible for digestive troubles which may ensue.

Bacterium coli infections of the genito-urinary tract frequently complicate chronic bacillary dysentery.

Reiter's disease.—The combination of conjunctivitis, arthritis and urethritis has been described as Reiter's disease by Fiessinger in France, Macfie in North Africa, and by Jackson and Wrigley (1946) in soldiers in the second World War. Some authors term it "pseudogonococcal arthritis." The conjunctivitis is purulent or mucopurulent, often bilateral, with photophobia and lacrymation. There may be iritis, scleritis and keratitis. The urethritis is characterized by a purulent discharge which is bacteriologically sterile. Arthritis usually affects the larger joints and is fugitive in character. Skin rashes are common and general lymphadenitis is a frequent accompaniment. The disease is characterized by tendency to multiple attacks with fever and raised blood sedimentation rate. There are usually circumscribed areas of tenderness on the periosteum. Reiter's disease is bi-symptomatic in less than 25 per cent. of cases. Usually conjunctivitis and urethritis are found together, but seldom urethritis and arthritis simultaneously. The resemblance to chronic bacillary dysentery is undoubtedly great, and there is still considerable hesitation in recognizing it as a separate disease. The virus has been claimed to have been cultivated by Dunham (1947) and has been found capable of producing conjunctivitis in mice.

Bacillary-dysentery carriers.—Dysentery bacilli, as a rule, are scarce and liable to escape detection in a faecal stool, though with improved methods of isolation by desoxycholate agar, the carrier rate has been assessed about 10 per cent. It is probable that carriers are the starting-point of an epidemic. The majority are "*convalescent carriers*," a term which implies that the patients have incompletely recovered, continuing to pass blood, mucus and dysentery bacilli in their stools. There is no

evidence that the gall-bladder acts as a reservoir, as in typhoid; or that the "carrier state" persists for any great length of time.

Carriers of Flexner bacilli are much commoner than those of Shiga. Generally, the Flexner carrier is in good health, while the Shiga carrier is adversely affected. Stewart (1944) found carriers of Flexner, Sonne and Schmitz organisms comparatively commonly amongst the native population of Algeria.

Diagnosis.—Difficulty in the diagnosis of bacillary dysentery on clinical grounds is mainly confined to the milder forms. Whenever possible, a confirmatory laboratory diagnosis should be carried out.

A tentative diagnosis may be made from a microscopic examination of the *cellular exudate* in the stools which is known as cytodiagnosis. For this purpose the specimen should be procured from the patient as early as is possible in the disease. The characteristic feature of bacillary stool (Plate XI), is the preponderance of swollen *polymorphonuclear leucocytes*, with distinctive ring-like nuclei, which constitute over 90 per cent. of the total cell elements in the stool. The examination should be conducted with a $\frac{1}{8}$ -in. lens and a low ocular ($\times 2$).

Macrophage cells (histiocytes).—These, sometimes 20–80 μ in diameter, are derived from the endothelium of the capillary vessels. They may be round, oval, or bilobed. They are hyaline, and contain in their substance vacuoles, fatty granules, ingested red blood-corpuscles, even, occasionally, leucocytes. They are non-motile, but, owing to their phagocytic activities, are apt to be mistaken for *Entamoeba histolytica*.

It is important that the significance of macrophage cells in bacillary dysentery stools should be emphasized. Willingness to diagnose amœbic dysentery is very pronounced in almost every tropical country. As there has been some confusion on the origin of cytodiagnosis as a secure and rapid method of diagnosis in bacillary dysentery, the Editor puts forward his claim to the originality of this work. Jürgens in 1907 described macrophages in bacillary dysentery. The Editor in 1910 confirmed the presence of these cells in the cellular exudate of bacillary dysentery and published a method of differentiating from amœbic and other forms of dysentery in 1912. The term cytodiagnosis was applied in the epidemic of bacillary dysentery in Gallipoli in 1915.

Entamoeba coli, and flagellate protozoa (*Chilomastix* and *Trichomonas*), may be seen in considerable numbers in a bacillary-dysentery exudate.

Isolation of the dysentery bacillus.—A portion of freshly-passed blood and mucus should be picked out by a platinum loop, and, if soiled with faeces or urine, should be rinsed in 5 ml. of distilled water or normal saline solution. It is, as a general rule, difficult when dysentery has lasted five days or longer. Faeces despatched for laboratory examination through the post, or by messenger over long distances, should be emulsified with a double volume of buffered glycerol saline—1 part of glycerine to 2 parts of saline, buffered by the addition of 5 per cent. acid sodium phosph., at pH 8. The mucus, or two loopfuls of the suspension, should be spread, in a spiral manner, upon a MacConkey agar plate, or, better, on desoxycholate citrate agar. The plate should be incubated at 37° C. in an inverted position for eighteen hours, when the small blue transparent colonies may be examined with a watchmaker's lens. As a rule, Shiga colonies are more refractile and of a more regular outline than are those of the Flexner-Boyd group.

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TABLE VIII

DIAGNOSIS BETWEEN BACILLARY AND AMOEBIIC DYSENTERY

BACILLARY DYSENTERIES	AMOEBIIC DYSENTERY
Acute diseases with a tendency to epidemic spread. "Lying down dysentery."	A chronic endemic disease. "Walking dysentery."
Incubation period short, 7 days or less.	Incubation period long; at least 20-90 days; may be more.
Onset acute.	Onset insidious.
Pyrexia common.	Pyrexia rare, unless complicated.
Course days or weeks.	Course usually prolonged for years.
<i>Complications</i> : Polyarthritides frequent; eye complications.	<i>Complications</i> : Hepatitis, abscess of liver; abscesses rarely in other situations. Pericolic abscess. Amoebic infection of skin.
Death due to—	Death due to—
(a) Exhaustion.	(a) Exhaustion.
(b) Toxæmia.	(b) Perforation.
(c) Glomerulonephritis.	(c) Haemorrhage.
	(d) Liver abscess.
<i>Signs</i> : Tenderness over whole abdomen, more marked over sigmoid flexure.	<i>Signs</i> : Local tenderness and thickening, mostly over sigmoid flexure, transverse colon, and cæcum.
Tenesmus very severe.	Tenesmus not usual.
<i>Pathology</i> : Acute diffuse necrosis of mucous membrane of large intestine, due to dysenteric toxins.	<i>Pathology</i> : Local lesions confined to the large intestine, due to the characteristic ulcers.
<i>Ulcers</i> : When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut.	<i>Ulcers</i> : Commence as small abscesses of submucosa in long axis of gut. "Flask-shaped ulcer," or " <i>Bouton en chemise</i> ," "sea anemone" ulcers.
Serpiginous in outline, with ragged undermined edges, often communicating with neighbouring ulcers; bases consist of granulation tissue.	Oval, regular, flask-shape in section, involving all coats; bases consist of necrotic black tenacious sloughs ("Dyak-hair" sloughs).
Intervening mucous membrane hyperæmic. Ulcers rarely perforate. No compensatory thickening of bowel-wall.	Not uncommonly perforate; compensatory thickening of bowel-wall. Intervening mucous membrane normal.
<i>Stools</i> : Scanty; many in number. Bright blood-red, gelatinous, viscid mucus, odourless, resembling red-currant jelly.	<i>Stools</i> : Fæces intermingled with blood and mucus, resembling anchovy sauce (sago-grain stool). Offensive, smelling of decomposing blood; generally copious.
<i>Reaction</i> : Alkaline.	<i>Reaction</i> : Acid.
<i>Microscopic picture</i> : Numerous red cells; polymorphonuclears numerous, with clear-cut ring nuclei, Macrophage cells. Few micro-organisms visible (Plate XI).	<i>Microscopic picture</i> : Red cells numerous and in clumps, polymorphonuclears damaged, often with extruded nuclei. Macrophage cells scanty. Large numbers of motile bacilli and <i>Entamoeba histolytica</i> , usually containing ingested red cells. Charcot-Leyden crystals common (Plate XII).
<i>Blood examination</i> : Leucocytosis in the early stages.	<i>Blood examination</i> : Usually a moderate leucocytosis.

water, rice water, chicken soup, beef tea, Brand's essence, arrowroot, Horlick's, Bengers, sago puddings—any of which may be given at two-hourly intervals in small quantities (6–10 oz.), slightly warmed. Non-residue diet should be instituted when blood and mucus have disappeared from the stools.

Sulphaguanidine, a specific drug, was first prepared by Buttle and colleagues, though Marshall and others described its chemical constitution. It exerts a bacteriostatic effect on various bacteria *in vivo* and *in vitro*. It is moderately soluble in water, insoluble in strong alkali.

The dosage of sulphaguanidine in acute bacillary dysentery was: initial dose of 0.1 grm. per kilo (or $9\frac{1}{2}$ gr. to the stone (14 lbs.) body weight), a maintenance dose of 0.05 grm. per kilo four-hourly for the period during which the number of stools exceeds five per day, and a further maintenance dose of 0.05 grm. per kilo every eight hours until the stools have been normal in number and consistency for two days. Duration of treatment should not exceed fourteen days. If necessary, the course might be repeated. In chronic bacillary dysentery larger doses were necessary: 0.1 grm. per kilo every eight hours for the first five days, followed by a dosage of 0.05 grm. for a similar period for another five days. This might be repeated in fourteen days. The total dosage in acute cases varied from 18 to 350 grm.; the average effective dose in acute cases was about 130 grm., usually between 100 and 200 grm. In less acute cases it should be 18 grm. in the first twenty-four hours, administered in 6 grm. doses three times daily, and subsequently 3 grm. three times daily for five days.

The effects might be judged by the alteration in the patient's general condition and in the improvement in the stools which, in most cases, become porridge and faecal in forty-eight hours. A diminution in temperature, pain and toxæmia took place within twenty-four hours. The mortality rate, in very extensive series reported upon from the Middle East, was less than 1 per cent. Sulphasuccidine appeared to be equally effective, especially in children. Sulphapyridine and sulphamezathine in maximal doses was also curative, but are more depressing and more toxic. According to Fairley and Boyd, sulphaguanidine treatment should be combined with preliminary dosage with magnesium or sodium sulphate and, after two hours, with gentle colonic lavage employing one pint of normal saline. Modern sulphonamides have superseded sulphaguanidine.

Other sulphonamides.—According to Ferriman, Mackenzie and Scadding, *sulphadiazine* is the drug of choice in the milder type of case, in doses of 1 grm. five times daily, and it cuts short long-continued diarrhoea.

Phthalyl sulphathiazole closely resembles sulphasuccidine, but is twice as active and is highly specific in Flexner and Sonne infections. The dose is 0.04 grm. per kg. every four hours for 12 doses, then 0.02 grm. at four-hour intervals until the diarrhoea ceases. The average period of clinical cure is 8.73 days.

Streptomycin, when given by the mouth, is specially effective in Sonne dysentery (Rivers, 1956). The preparation known as guanimycin contains streptomycin 0.25 grm. sulphaguanidine 2 grm. per fluid ounce. Out of 82 cases of Sonne infection 20 became negative in less than one

week. Sonne's bacillus is very sensitive to streptomycin *in vitro*. Sulphathalidine is considered by some to be the most efficient sulphonamide in Sonne infections.

Chloromycetin (chloramphenicol).—Ross and colleagues have demonstrated the sensitivity of Shiga bacilli to chloramphenicol *in vitro* and its efficacy in dysentery in children. Ninety-six cases in Hong Kong from January to December, 1951, were treated with chloramphenicol (average total dose 9.5 gm.—individual doses ranging from 7.75–16 gm.) which checked the dysentery in three days.

Antidysenteric serum.—Since the introduction of sulphaguanidine the value of antidysenteric serum has been discounted. It is now employed principally in toxic Shiga cases.

Relief of pain.—During the early stages of an attack the patient may suffer much from griping and tenesmus. Tenesmus and dysuria are best relieved by hypodermic morphia; by an enema of a wineglassful of thin starch containing 40 or 50 drops of tincture of opium; or by suppositories of morphia and cocaine. Washing out the lower bowel with a pint of hot water, with or without boric acid, is sometimes effectual in removing for a time, or, at all events, mitigating, the incessant desire to go to stool and to strain. Bismuth carbonate, 2 dr., with tincture of opium, 30 min., and thin starch, 2 oz., is also a good sedative enema.

Collapse from dehydration and vascular failure may occur at almost any stage. An attempt should be made to restore the balance by intravenous injection of large quantities of saline and glucose. Blood and plasma transfusions have been employed in these cases with striking benefit during the second world war.

Treatment of complications.—*Arthritis* is best treated by application of Scott's dressing and radiant heat.

Sulphasuccidine treatment appears to be specially efficacious.

When the joint is greatly distended the excessive fluid may be aspirated.

Streptomycin has been given (1951) in doses of 0.5 gm. twice daily for 21 days with good results (Chaudhuri).

Iritis is treated by atropine, the use of an eye-shade and the usual measures.

The treatment of chronic bacillary dysentery has been radically altered since the introduction of the sulpha drugs, which should be given in full doses over a prolonged period of fourteen days or longer. Fairley and Boyd, by periodic sigmoidoscopic examination, observed healing of chronic ulcers, and even those with exuberant granulations and pseudopolypoid appear to do well, but it is often necessary to repeat the course of sulphasuccidine. In refractory cases it may be necessary to inject the sulphonamide by retention enemata, in doses of 7–10 gm. daily, suspended in water and mucilage (7–10 ounces). This medicated enema is retained from three to four hours.

Cæcostomy and ileostomy.—In cases with pseudopolypoid of the mucous membrane and incessant distressing blood-stained diarrhoea, ileostomy may be resorted to.

Granular rectitis is best treated with suppositories of sulphasuccidine (Cluer, 1947). These suppositories are longer and bigger than those

usually supplied. They are composed of succinyl sulphathiazole 8 grm., cocoa butter 7 grm.

The powdered succinyl sulphathiazole is placed in a warm dish and half the quantity of cocoa-butter added. The ingredients are stirred to form a smooth paste before the rest of the cocoa-butter is added. When poured into moulds and set, the finished product is over 2 in. long and $\frac{1}{2}$ in. in diameter. For this special glass tubes are made. These are lubricated inside with almond oil and corked at one end. A palliative drying paste (Siccolam) is applied to the weeping areas of circumanal skin and in the anal canal (Barclay).

Prophylaxis.—The prophylaxis of bacillary dysentery consists principally in securing a pure water supply and in avoiding unwholesome and contaminated food; also in eliminating flies from latrines and in protecting food against them. In barracks, camps, lunatic asylums, and other public institutions, bacillary dysentery should be regarded as an infectious and readily communicable disease, and therefore patients suffering from mild symptoms, or even looseness of the bowels, should be isolated.

Chemoprophylaxis.—In the closing stages of the 1939–1945 war in the Far East sulphaguanidine, in doses of 1 grm. daily, was employed for mass treatment of troops in the field with apparent success.

The treatment of carriers.—The sulpha drugs should be given in maximal doses for periods of 5–7 days, though it is usually necessary to repeat the course. For it to exert its maximum action, the faeces must be kept as fluid as possible by means of sodium or magnesium sulphate. Carriers of Sonne's bacillus appear to be especially difficult to cure (*see p. 459*).

II. AMŒBIC DYSENTERY AND AMŒBIASIS

Definition.—Amœbiasis denotes infection with the protozoan, *Entamoeba histolytica*. When confined to the intestinal canal it produces *amœbic dysentery*, or primary intestinal amœbiasis. This is insidious in its onset, chronic in its course, and with a marked tendency to relapse. When metastatic lesions are produced in the liver and elsewhere they should be known as secondary, or *hepatic amœbiasis*.

Geographical distribution.—Amœbiasis occurs to a greater or lesser degree throughout the tropics and subtropics. During recent years sporadic indigenous cases have been found in Northern Europe (Russia, Norway and Germany) and even in Great Britain. Specially prevalent in India, Indo-China, China, and the Philippines, it is common throughout North and Central Africa, widespread in the Southern United States, South America, and the West Indies.

Epidemiology and endemology.—A disease of insanitation, not necessarily requiring tropical or subtropical conditions for its propagation, amœbiasis arises sporadically without seasonal prevalence, but does not usually occur in epidemic form in the same manner as the bacillary dysenteries. Wenyon and O'Connor have shown that the cysts of *E. histolytica* can be demonstrated in the faeces of houseflies sixteen hours after ingestion, and that flies play a part in dissemination. Roberts (1947) has demonstrated *E. histolytica* cysts also in the fly's vomit. The evidence

is that they are not derived from the crop, but represent those which become wedged in the pseudo-tracheæ and are later flushed out by fluid from the crop or from the salivary glands. There is also much evidence that *contaminated water* and even fresh vegetables, such as lettuce, may constitute sources of infection.

It has now been shown that wild rats, especially *R. norvegicus*, are frequently infected with *E. histolytica* and may aid in its dissemination (Neal, 1948). This has been confirmed (1951). *E. muris*, a species indigenous to the rat, closely resembles *E. histolytica*; also *E. moshkovskii*, a free living form. The entamoeba of snakes may mimic *E. histolytica* very closely (see Appendix, p. 930).

Reports of the outbreak in Chicago in the summer and autumn of 1933 gave the total number of cases as 1,409, in that city or traced to others in the United States, with over 40 deaths. The source was traced to two hotels, where the majority of those infected were servants or guests. All carriers of *E. histolytica* were removed from employment, but in spite of these measures, cases continue to develop amongst employees of one hotel, where the "carrier" rate was found to be as high as 47·4 per cent. Further investigations revealed serious contamination of the water supply from defective drainage so that drinking water formed the main channel of infection. Morton and associates (1952) have recorded an outbreak of acute amoebic dysentery in an R.A.F. camp in England as the result of gross faecal contamination of a water bore-hole. In a population of 1,042 at risk, 141 suffered from acute gastro-enteritis, 6 developed acute amoebic dysentery and 11 active amoebiasis of less severity. The majority had never been overseas. Twenty-six symptomless cyst-passers were found. Following a small outbreak of amoebiasis in a factory as a result from sewage contamination of a water supply in South Bend, Indiana, the incidence amongst employees was 52·4 per cent. compared with that of 4·4 per cent. in a neighbouring plant (Brooke, 1956).

Amoebic dysentery is frequently a house or family infection as shown in the Liverpool outbreak reported by Adams and Seaton (1949). In fact in U.S.A. multiple infections within a family group are the rule rather than the exception. When one individual is found infected with *E. histolytica* the probability is that 60 per cent. of his family may be infected also (Mackie, 1956).

Intestinal amoebiasis is a disease of adult life as a rule. It is rare in European children under five years of age, but among Egyptians of the poorer class in Cairo, Perry and Bensted found that 13 per cent. of clinical dysentery was due to *E. histolytica*. Biggam diagnosed acute amoebic dysentery with liver-abscess in an infant three months old, and Williams found it in a negro infant of fifteen months on the Gold Coast. In Durban, amongst the Zulus, infantile amoebiasis is extremely common. Children, under a year old, have acute amoebiasis and quite frequently, amoebic abscess of the liver. As the disease has a long incubation period and is acquired from contaminated water and vegetables, it is unlikely to occur among carefully nurtured children, in whom the bacillary form is more frequent. That insanitary surroundings and insanitary habits are potent factors in the spread of amoebiasis is seen in its frequent occurrence in lunatic asylums. Thus Cooper and others have determined that the incidence of *E. histolytica* cysts in the faeces of mentally-deficient children in Institutions in the vicinity of London is almost 50 per cent.

Intestinal amœbiasis may produce active symptoms for many years. The Editor has treated infections which have persisted from thirty to forty, and in one for fifty-four, years without seriously undermining health, so tolerant are the tissues to *E. histolytica*. There appears also to be a difference in incidence of intestinal amœbiasis in the sexes. Males, European and native, are more apt to contract the infection. Gharpure and Saldanha (1930) reported that in a series of over 400 post-mortem examinations the number of male cases was quite disproportional to the total. Of amœbic dysentery and liver abscess, 90.6 and 93.8 per cent. respectively occurred in males; 9.4 and 6.2 per cent. in females. Below ten years of age the incidence of amœbic lesions was 0.9 per cent. and of liver abscess nil. The highest peak is reached in the decennial periods 20-40, with a proportion of about 30 per cent. of amœbic dysentery and 38 per cent. of liver abscess to the total number of autopsies.

In Armenia, Zaturjan showed that amœbiasis in children usually runs a much more benign course than in adults and rarely shows any serious complications.

The question of enhanced virulence of strains of *E. histolytica* has been raised. It has been shown by Elsdon-Dew that, amongst the multi-racial inhabitants of Durban, the incidence is greatest in the urban Bantus who live normally on a protein-deficient diet which favours invasiveness of *E. histolytica*, whereas in the rural African, whose food consists of crude starches, amœbic infection usually runs a symptomless or mild course.

Ætiology.—The discovery of amœbæ in dysentery stools was made by Lösch in 1875. Originally regarded as a single organism—*Amœba coli*—it is now recognized, mainly as a result of the work of Schaudinn, Hartmann, Wenyon, and Dobell, that several distinct species occur in the intestinal canal of man, one of which, *Entamœba histolytica*, is pathogenic, while others—*Entamœba coli*, *Endolimax nana*, *Iodamœba bütschlii* and *Dientamœba fragilis*—are harmless species. *E. histolytica* was originally cultured on egg-medium by Boeck and Drbohlav in 1925, but during the last few years it has been grown on a variety of serum-media. *E. histolytica* can be grown in microtubes in symbiosis with *Trypanosoma cruzi*. For successful culture the presence of bacteria is necessary, although excystation can take place in the absence of bacteria when complex organic substances are added to the medium. *E. histolytica* grows anaerobically better in the tissues of older chick embryos than in those of younger ones. It is emphasized that in this tissue culture no other organisms than *E. histolytica* are present.

Detection of *Entamœba histolytica* in stools.—When present in stools, entamœbæ are generally easy to detect. It is necessary to pick out a small fragment of stool shortly after it is passed, and to lay it on the slide and compress it under the cover-glass to form a fairly transparent film. Active entamœbæ tend to occur in clumps or masses and are not evenly distributed throughout the stool; they may be present in one evacuation, but not in the next. Care should be taken that the receptacle in which the stool is collected is free from all traces of antiseptic. These amœbæ live in the fæces for a few hours after being passed and are distorted in the presence of urine. The dysentery amœba is a clear, faintly greenish-tinted, transparent body, as a general rule, some three to five times the diameter of a red blood-corpuscle. By staining the background with dilute eosin the refractile appearance of *E. histolytica* becomes more apparent. In its vegetative or tissue-invading phase it is recognizable by its active movements, as well as by the presence of extraneous material, such as red blood-corpuscles, which it ingests. The nucleus may sometimes be eccentric. The habit of ingesting red blood-corpuscles and body-tissue cells is one of the points of distinction between *E. histolytica* and non-pathogenic *E. coli*.

In fresh and in stained preparations¹ the amoeba is seen to be made up of two zones—a granular endoplasm surrounded by a clear protoplasmic ectoplasm. The nucleus shows a characteristic uniform structure, if the specimen is fresh and fixed while alive; aberrant forms with fragmented karyosomes, etc., are due to degenerative changes (see p. 456).

These amoebæ flow, rather than move, across the slide, and in the living state do not always exhibit conspicuous differentiation between ectoplasm and endoplasm as described. They quickly die and degenerate outside the body. At lower temperatures they remain stationary, but when the slide is warmed, they eject from time to time hyaline “blade-like” pseudopodia (Fig. 83). Degenerating entamoebæ often contain vacuoles, but these are not normally present. When conditions become adverse, they encyst, first passing through a precystic stage.

Cysts.—Cysts vary much in size. They contain highly refractile masses of chromatin, or chromatoid bodies, which may assume the form of blocks with rounded ends, and also glycogen-containing vacuoles. When first formed, the cyst contains one nucleus, which measures about one-third of its diameter. This divides by binary fission, so that finally, in the more mature individuals, four small nuclei, each measuring one-sixth of the diameter of the cyst, are produced. In general characters the nucleus of the cyst resembles that of the vegetative stage.

Cysts of *E. histolytica* can survive outside the body of man for about ten days, if kept moist and cool. Desiccation kills them immediately, though they survive much longer at lower than at higher temperatures.

Westphal has recorded a significant experiment where an apparently harmless *E. histolytica* infection was acquired by the ingestion of cysts. Some months later cultures of bacteria isolated from the fæces of acute amoebic dysentery were ingested and a similar dose was given to a control. Both the “carrier” of *E. histolytica* and the control suffered from diarrhoea, but on the twenty-third



Fig. 83. Camera lucida drawings showing protrusion of pseudopodia by *Entamoeba histolytica*. (P.H.M.-B. del.)

day, the former developed clinical amoebic dysentery. It was finally determined that super-infection with Flexner bacilli excited the clinical manifestations of amoebic dysentery. Some workers therefore believe that symbiotic bacilli aid, or in some way instigate, attacks of acute amoebic dysentery. This view has been to a great extent confirmed by Hoare (1949), who has shown that in the great majority of cases the amoeba is coprozoic and feeds on bacteria and faecal debris. In *amoebic dysentery*, however, it feeds on erythrocytes. In experimental infections of rats it shows every gradation from a commensal life to true parasitism. In monkeys *E. histolytica* usually produces a symptomless infection and feeds on micro-organisms, whilst in cultures it may ingest starch granules. In addition to this method of nutrition *E. histolytica* takes up food saprozoically by absorption of fluid through the surface of its body. It is now generally

¹ For the staining of amoebæ in liquid preparations, Schaudinn's method is employed. The details of amoebæ are distorted if attempts are made to dry the specimen as in a blood-film.

recognized that the small race is non-pathogenic and is known as *E. hartmanni*. Minor morphological differences can be recognized in the nuclei.

Most clinicians consider that *E. histolytica* is an obligatory parasite, but it does live commensally *in vitro* in cultures and can exist commensally *in vivo* in monkeys. Symptomless human carriers of the infection discharge amœbæ containing bacteria, but no red cells, which indicates a commensal habit. Sigmoidoscopic examinations of "carriers" reveal no lesions in the gut wall and, furthermore, at post mortem the bowel is unscathed. Symptomless carriers may discharge 350,000 non-hæmatogenous amœbæ per grm. of fæces (or 85 million parasites daily). Furthermore, after purgation, which causes the discharge of numerous amœbæ, the number of cysts in the stools is lessened suggesting that the parasites have been swept from the lumen of the gut.

Occasionally, however, vegetative amœbæ migrate from their site in the bowel-wall and, as tissue-invading forms, enter the venous system and are transported to the liver, exceptionally to the spleen, brain or lung; but by so doing they become unable to complete the cycle of development as observed in the intestine, for pre-cystic individuals and cysts are never produced in these situations. Amœbic infection of the skin has been seen quite often (see p. 497).

E. histolytica passers.¹—The healthy passer (or excretor) of *E. histolytica* is an individual who has not suffered, and is not suffering, from dysenteric symptoms, but passes *histolytica* cysts, though otherwise in good health. Such cyst-passers may, or may not, have active entamœbæ in the tissues of the bowel.

The cyst-passers may be divided into two classes—(1) *contacts* who have never suffered from clinical amœbic dysentery, and (2) *convalescents* who have recovered from an attack. It is known that, for every abnormal person who is suffering from amœbic dysentery with passage of vegetative forms which are non-infective to other individuals, there are large numbers of healthy persons who continue to pass *E. histolytica* cysts, thus constituting a perennial source of infection. It is thought that in the first case the parasite lives in the fæces, or is commensal, in the second it continues to persist in the tissues of the host (the action of diodoquin on the parasite may afford the correct interpretation (see p. 479)).

The lesions of the mucosa may be microscopic. Cytolysis and necrosis of the epithelium is followed in the majority of instances by rapid regeneration, so that probably only a small percentage develop clinical evidences of amœbic dysentery. The experiments of Walker and Sellards showed that, out of 20 men fed with *E. histolytica*, 18 became parasitized, but only 4 developed dysenteric symptoms, though the remainder continued to pass cysts in their stools.

By intrarectal and intracæcal injection of fæces containing cysts into cats and puppies, ulceration of the bowel-wall and hepatic abscesses have been produced; but, although the fæces may be swarming with active vegetative forms, no cyst-formation has ever been observed in these animals.

¹ "Cyst-passer" is here used in the place of "carrier," a term which is not strictly applicable to *E. histolytica*.

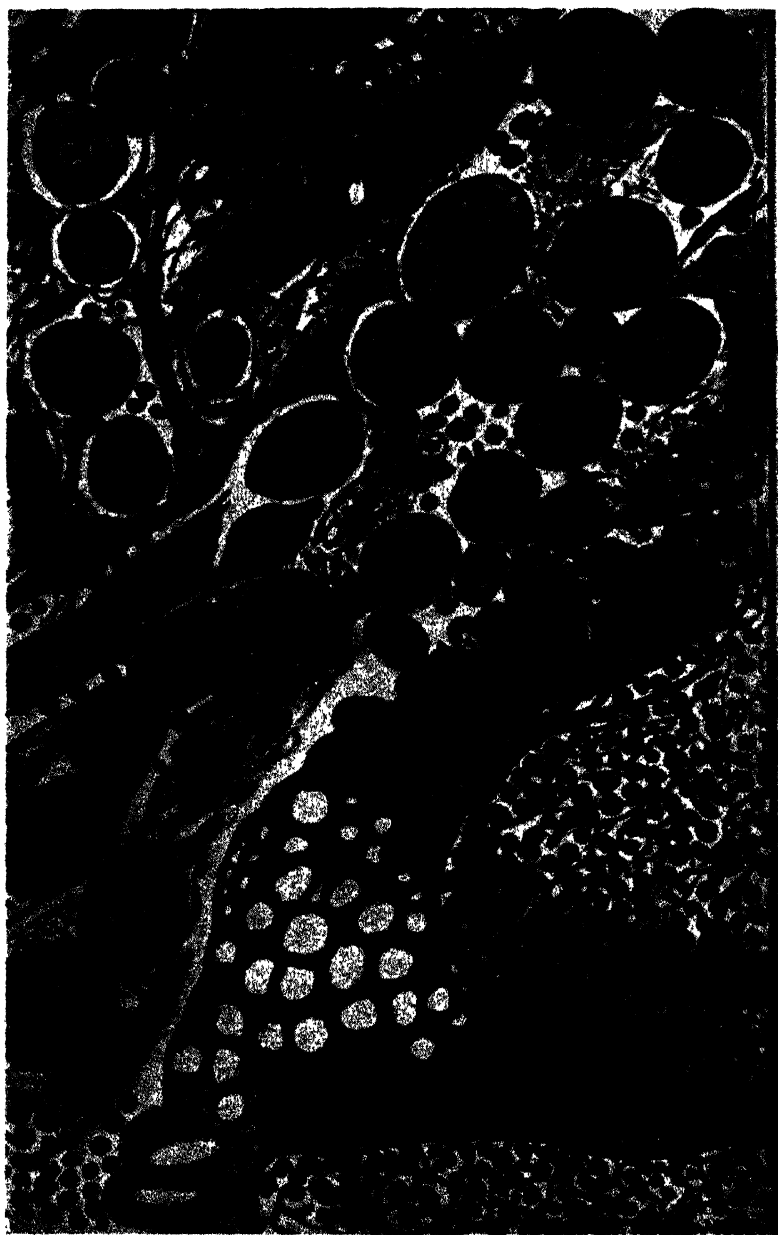
Intracæcal injection of young white rats with cultures of *E. histolytica* has proved in recent years a valuable method of studying this parasite and the action of specific drugs upon it (W. R. Jones, 1946; L. G. Goodwin, 1947). By these means they have shown that strains from different sources vary in their infectivity and that pathogenicity does not depend upon the number of amœbæ injected, or upon the severity of the human infections from which they were derived.

Incidence of cyst-passers or carriers.—Among British soldiers after a year's service in Egypt, Wenyon and O'Connor found that there was no marked difference between carriers who had previously suffered from dysentery and those who had not (the percentages being 6·5 as against 4·5 per cent.). The carrier rate among native Egyptians, as might be surmised, was considerably higher, 13·5 per cent. The most surprising outcome of the systematic examination of fæces by protozoologists during the 1914–1918 war was the almost universal presence of the *histolytica* carrier. Yorke, Matthews and Malins Smith found a considerable percentage of carriers among lunatics, army recruits, and the personnel of the navy in England. The two former recorded 5 per cent., the latter 19 per cent.: Kuenen found a considerable number of indigenous infections in Holland, and Brug estimated the carrier-rate as 12·7 per cent. in that country. In the United States amongst schoolchildren it may be as high as 10·8 per cent., but in adults Andrews and Paulson gave a much lower figure, 0·2 per cent. In New York City it was 1·1 per cent. among city dwellers, 5·4 per cent. among foodhandlers, and in Philadelphia 5·2 per cent. for the general population. Craig has estimated that 10 per cent. of the total inhabitants of the United States were infected with amœbiasis. The exact significance of these figures is difficult to determine. It certainly does not mean that this comparatively large number is suffering from gross ulceration of the bowel, for indigenous *amœbic dysentery* is very uncommon in England. Even among the insane, with a relatively high cyst-passer rate, "clinical amœbic dysentery" is rare. Belios and Cooper (1953) have now proved that in mentally deficient children in Hertfordshire the incidence of *E. histolytica* infection may be 40 per cent.

A single microscopic examination probably detects one third of the cases so that the true percentage of "carriers" in a normal population is about 10 per cent. for *E. histolytica*, 36–54 per cent. for *E. coli* and 13 per cent. for *Endolimax nana*. Infection is probably acquired at an early age. Evidence suggests that infection of the same order occurs in France, Holland, Germany and other European countries, yet amœbic lesions of the intestine and liver are rarely found.

Pathology.—The earliest lesions of amœbic dysentery are minute yellow hemispherical elevations of the mucosa, which mark the site of a deeper-lying zone of necrosis. By growth in size and localized necrosis they form flask-shaped ulcers, the bases of which lie in the submucosa. These ulcers are scattered throughout the large intestine, rarely extending above the ileo-cæcal valve. The appendix may be involved, and Musgrave, in 1910, reported three cases of fatal peritonitis due to this; since then a few other cases have been investigated in which entamœbæ were demonstrated in microscopic sections. Amœbic ulceration of the ileum has been described by Biggam. These were acute and rapidly fatal cases, and in neither instance were amœbæ demonstrated in the stools, but in preparations from the lesions.

The ulcers may not be larger than a pin's head or may measure an inch or more in diameter, and, as the disease progresses, may become even larger. Then the margins are rolled, the edges undermined, and the base is formed by fibres of the muscular coat (sea-anemone ulcers). The ulcers are capped by dense yellow, green, or even black sloughs (Dyak-hair sloughs), which may project into the lumen of the bowel (Plate X, Fig. 1). The lesions usually originate in



Entamoeba histolytica entering a crypt of Lieberkuhn. (Kohn's stain) X 1,000
(P. Manson-Bahr)

PLATE XI

the cæcum, are scattered throughout the transverse, sigmoid colon and rectal canal. Usually the intervening mucous membrane remains healthy. Amœbic lesions commonly extend throughout the large intestine as far down as the internal anal sphincter.

In 186 cases examined *post mortem* by Clark in 1924, lesions were scattered throughout the colon in 61 per cent. affecting, in order of frequency, cæcum, ascending colon, iliac colon, sigmoid, rectum and hepatic flexure. At the sites where intestinal stasis is greatest there is a tendency for amœbæ to invade the bowel wall.

Sellards and Leiva demonstrated in experimental animals that when the cæcum is exposed and infective material is introduced into the lumen, infection takes place with surprising regularity, but that, whether it is introduced directly into the cæcum or *via* the rectum, initial lesions occur in the extreme lower part of the bowel. Stasis in the large intestine affords the organisms a foothold, and is a factor in determining the location of the initial lesion. Wagner and Beiling, whose conclusions are almost identical, found that the amœbæ at these focal points enter the tissues in one of three ways, passing directly into connective tissue, crypts, or lymph-channels, where they migrate to the lymph-follicles and the submucosa. The intestinal mucosa responds to invasion by secreting mucus, which, when mingled with blood, forms an excellent medium for the development of amœbæ on the bowel surface. The balance between host and parasite is delicate.

Thrombosis of the blood-vessels, in which entamœbæ are often found, occurs at the bases of the ulcers, and, by erosion, an arteriole may be opened, and severe or fatal hæmorrhage may result. Perforation by ulcers, even massive gangrene, especially of the cæcum, may also occur, and lead to fatal peritonitis. The ragged ulcerated mucosa becomes readily infected with pyogenic organisms.

In the healing gut, cicatricial pigmented scars mark the sites of former ulcers. Adhesions may form between proximal coils of intestine which become matted together or adherent to the liver and spleen. Pericolic abscesses may also sometimes form.

In chronic cases, polypoid or gangrenous tags project into the lumen of the gut. The intestinal contents may be composed of dark, almost black hæmorrhagic faecal matter with characteristic penetrating odour.

In the last years considerable attention has been paid to the amœboma, or amœbic granuloma, which results from repeated amœbic invasion of the colon with superadded pyogenic infection, producing progressive inflammatory lesions. This process spreads through the bowel wall into the pericolic and perirectal fat, infiltrating the surrounding structures. The resulting tumour consists of fibrous tissue, granulations and varying degrees of ulceration. The usual sites are the rectum, recto-sigmoidal junction and cæcum. Differentiation from carcinoma may be difficult.

Histology.—The amœbæ work their way down the crypts of Lieberkühn, multiply, and, by secretion of cytolytins, disintegrate the tissues of the sub-mucosa and produce gelatinous necrosis, with little surrounding tissue reaction and round cell infiltration (Fig. 84). In more advanced lesions the entamœbæ may be seen between the muscular fibres and within the peritoneal veins, whence they may be swept as emboli into the portal vein, lodge in the liver, and so become the starting-point of amœbic hepatitis or liver abscess (Plate XI).

The superficial layers of the slough of an amœbic ulcer become secondarily invaded by bacteria, though the adjacent mucous membrane remains healthy and shows few microscopic changes. The precystic forms of *E. histolytica* are found in the intestinal mucus and on the surface of the bowel.

Experimentally-produced amœbic dysentery in kittens differs essentially from the disease seen in man. When introduced into the rectum of the cat,

entamoebæ produce acute inflammation within two to three days. The lesions differ in their generalized and acute character from those observed in man. Death takes place from secondary terminal bacterial invasion. Cysts are never found, and chronic ulceration does not occur.

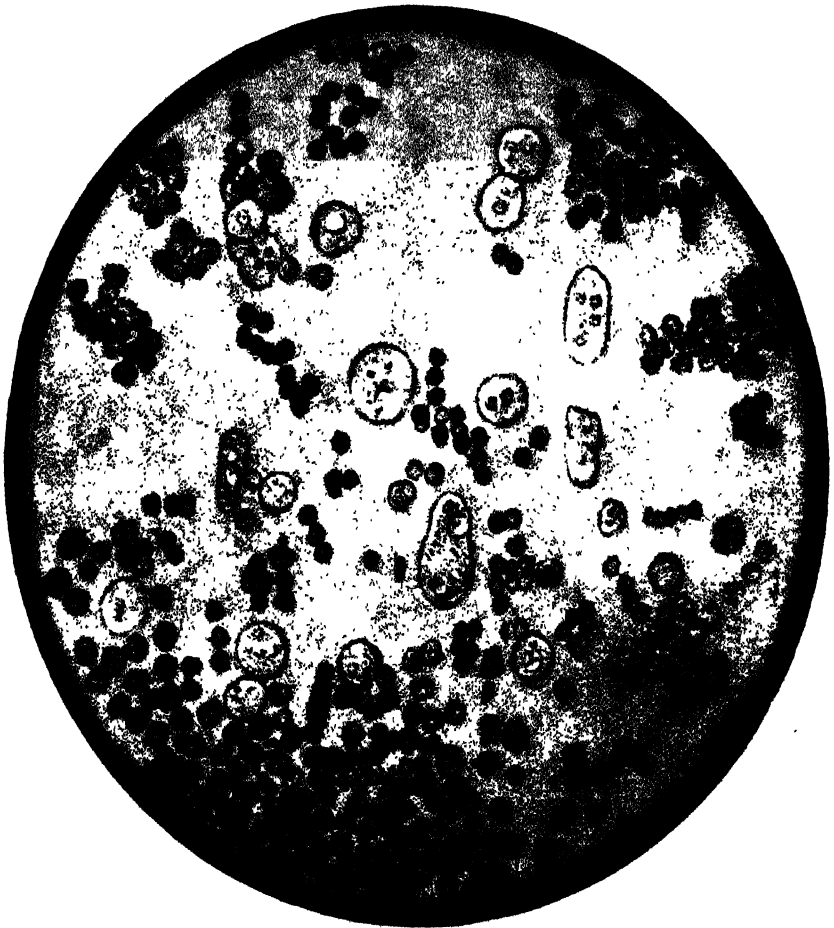
Symptoms.—The *incubation period* of amoebic dysentery, from the time of introduction of the cysts into the intestinal canal until the development of symptoms, may be of considerable length. In the Chicago outbreak of 1933 it ranged from seven up to seventy-seven days, symptoms appearing



Fig. 84.—Section through base of amoebic ulcer, showing *E. histolytica* in the tissues.
(C. M. Wenyon.)

occasionally within one week though, in a few instances, not for three or four months. The fact that amoebic cysts are found in the faeces of individuals who may never have had "dysentery" in the ordinary accepted sense, suggests that the development of clinical symptoms may possibly depend upon some secondary bacterial infection.

The great majority of cases of amoebic dysentery run a chronic course, with frequent intermissions and relapses. This latency is one of the most striking and characteristic features. The *onset* is generally insidious, so that the patient may complain more of diarrhoea than of dysenteric

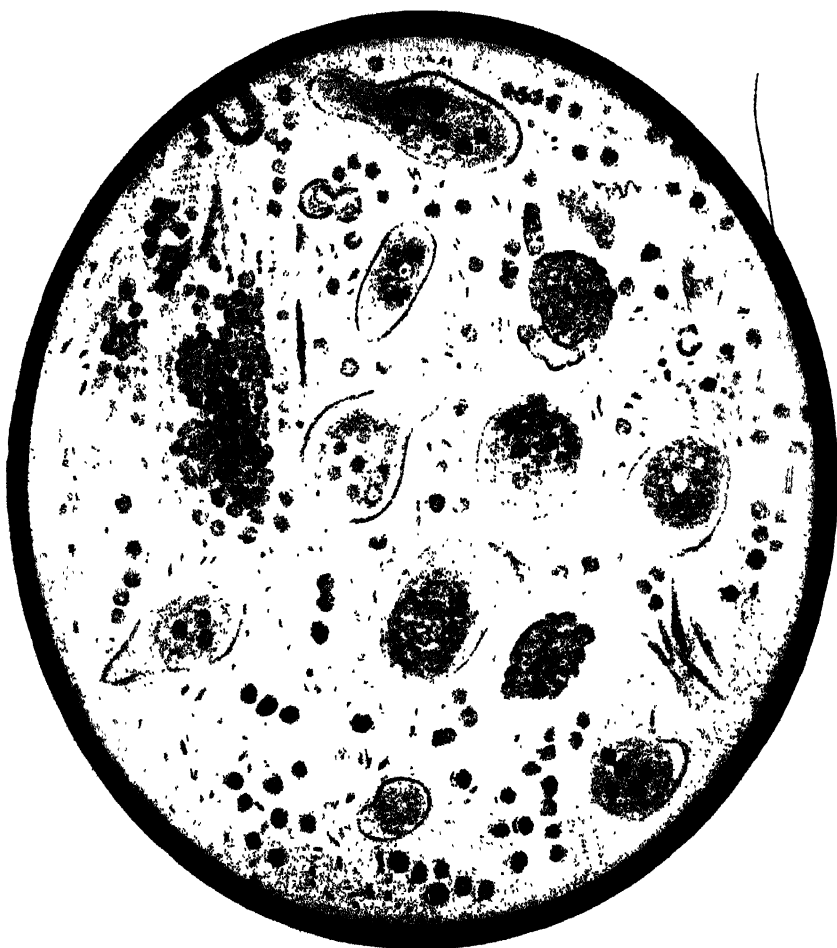


**MICROSCOPIC APPEARANCE OF CELLULAR EXUDATE
IN ACUTE BACILLARY DYSENTERY (Shiga infection)**

Fresh preparation. Shows macrophage cells with ingested red blood-corpuses,
intestinal epithellum and polymorphonuclear leucocytes.

(P. Manson-Bahr)

PLATE XII



**MICROSCOPIC APPEARANCE OF EXUDATE IN AMOEBIC
DYSENTERY**

Fresh preparation. Shows active *Entamoeba histolytica*, some with ingested red blood-corpascles: acicular Charcot-Leyden crystals and disintegrated intestinal epithelium.

(P. Manson-Bahr)

PLATE XIII

symptoms. Perforation of the bowel, leading to fatal peritonitis, has been known to occur in patients who, judged by clinical appearances, were not suffering from dysentery. In mild cases the patient generally complains of suddenly developing *amœbic diarrhœa*.

The symptoms, subjective and objective, may closely resemble those of bacillary dysentery; but, as a rule, abdominal tenderness is much less acute, and may be restricted to the cæcum, thus simulating appendicitis, or to the transverse colon, where it may mimic gastric ulcer; more frequently, however, it is limited to the sigmoid flexure. Should ulceration occur in the rectum, tenesmus and straining may ensue. The individual stools are bulkier than those of bacillary dysentery. They may not exceed three or four in the twenty-four hours, but are seldom more than twelve. As a rule, they contain much dark and altered blood, which exudes a penetrating, disagreeable odour. In consistence and appearance they resemble *anchovy sauce*. Often, blood-streaked mucus is intermingled with liquid fæces. Melæna may occur occasionally. The motions may sometimes be formed, and streaked with blood and mucus. Gangrenous sloughs may be voided. Unless the case is complicated by hepatitis, when the liver is painful and enlarged, there are seldom any toxic manifestations. *Acute* cases of amœbic dysentery with high fever and urgent painful and severe clinical manifestations are rare. In the Chicago epidemic acute cases of unusual severity, with pyrexia and other toxic manifestations (amœbic fever), were noted.

The patient, as a rule, becomes emaciated, but some remain in remarkably good condition, although suffering from repeated relapses. Some there are who even become grossly fat. Sometimes the skin is myxenoid and the complexion assumes a subicteric tinge. The tongue is moist and coated. Vomiting may rarely occur. Generally there is a complete anorexia. Dysuria is not noted as in bacillary dysentery, and *tenesmus* is rare. The *liver* is sometimes enlarged, even in the absence of hepatitis.

In uncomplicated amœbic dysentery, there is usually no pyrexia, but cases with intermittent fever are occasionally met and with high continued fever (amœbic fever), in absence of any ascertainable complications, and these may be recognized by amenability to emetine treatment by the discovery of amœbæ or cysts in the fæces, or by recognition of amœbic ulcers by sigmoidoscopy. In amœbic dysentery there is usually a moderate leucocytosis (10,000–12,000 with low proportion of polymorphonuclears—about 70 per cent.).

There still remain a number of obscure conditions of which some mention must be made. It is probably true, so variable are the symptoms of amœbiasis, that almost any intestinal disease may be simulated. Intestinal amœbiasis is *not invariably associated with dysentery or diarrhœa*. It may occasionally be marked by constipation, by lower abdominal pains or disturbances, very often by neurasthenia, bodily and mental lassitude, furred tongue, and disordered digestion, popularly described as an “uncomfortable belly,” or “growing abdomen.” Acute upper abdominal pain, with vomiting, is not suggestive of amœbiasis. Pathological changes in the bowel may sometimes lead to sacculation or even dilatation of the colon. Very often the cæcum is distended with gas and the source of

much discomfort. In chronic cases, diffuse infiltration of the sigmoid colon, less commonly of the cæcum, can be detected by abdominal palpation.

In the course of prolonged chronic amœbiasis, myxenoid cachexia may ensue, suggesting intestinal toxæmia. These patients have muddy complexions resembling in outward appearances some cases of diverticulitis.

Often, without treatment, symptoms may subside, and the patient may be apparently cured, but will relapse after an interval of weeks, months, or even seven years or longer. More often he continues to pass loose, semi-formed stools. Attacks of diarrhœa alternate with constipation. After any physical exhaustion, chill, alcoholic or dietetic indiscretion, a fresh exacerbation may supervene. On account of these variable symptoms, the infinite variety of abdominal pain, and the occasional melænic stools, it is clear that amœbic dysentery has to be differentiated from duodenal ulcer, gall-bladder disease, diverticulitis, pancreatitis and neoplasm.

Amœbic typhilitis.—Amœbiasis of the cæcum may be present without involvement of any other portion of the large bowel. This gives rise to local pain and deep tenderness. Differentiation from appendicitis may be difficult. As a rule, the local signs in the right iliac fossa predominate over the generalized signs of toxæmia, as in appendicitis.

Amœbic granuloma or amœboma.—The discovery of a sausage-shaped abdominal tumour in a subject of amœbic infection suggests this possibility. Such a tumour may be present in the cæcum, transverse colon, sigmoid or rectum. It may even be the cause of chronic intussusception, especially when situated at the apex of the cæcum (Ogilvie). It is usually hard and indurated, but tends to vary in size from day to day. Differentiation from carcinoma or tuberculoma may prove difficult when *E. histolytica* cysts may be absent from the fæces.

Hepatitis.—Acute amœbic hepatitis may supervene at any time during the course of amœbic infection, while the symptoms are acute, or during a remission. The patient usually experiences pain over the hepatic area, together with signs of toxæmia and pyrexia. His attitude is characteristic: he inclines to the right trying to protect his liver, carrying it in his hands, so to speak. The liver itself is enlarged; it may project below the costal margin to the level of the iliac crests, and then be extremely tender. Pain referred to the right shoulder, due to stretching of the diaphragm, is also frequent. Usually there is a leucocytosis of twenty to thirty thousand with low proportion of polymorphonuclears. A chronic form of amœbic hepatitis without pyrexia or leucocytosis is also recognized.

Hepatitis may subside without any active treatment. There is some evidence that in these cases the amœbæ are distributed throughout the liver, with embolic spread, suggesting a portal distribution. Fortunately this hepatitis is particularly amenable to emetine treatment and chloroquine (see p. 494).

All intergradations occur between acute and painful enlargement of the liver to the firm and practically painless chronic stage. The latest contribution to this subject is by Kean (1956), who had at his disposal 148 fatal

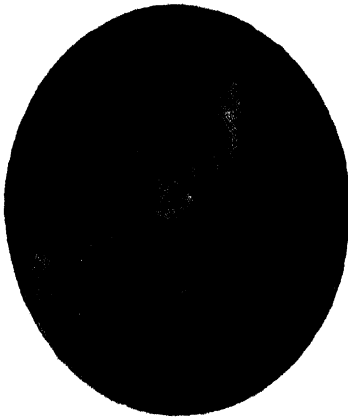


Fig. 1.—Acute bacillary dysentery (Shiga infection). Note œdema of mucosa and submucosal hæmorrhages.

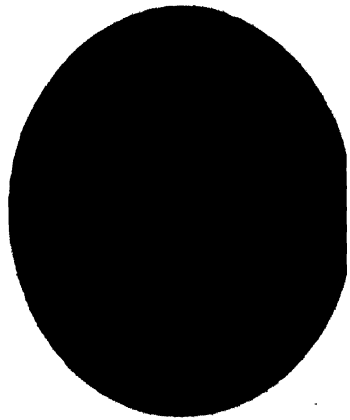


Fig. 2.—Chronic bacillary dysentery (Flexner infection). Note granulations on mucous membrane.

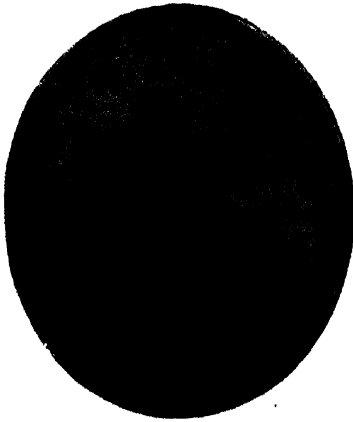


Fig. 3.—Acute amebic dysentery. Note folding of lax mucous membrane, pin-point ulcers and surrounding submucous hæmorrhages.

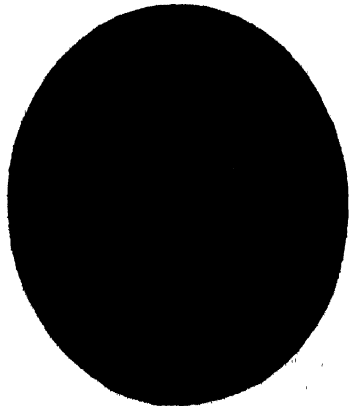


Fig. 4.—Chronic amebic dysentery. Note diamond-shaped ulcers and submucous hæmorrhages.

(*P. Manson-Bahr*)

SIGMOIDOSCOPIC APPEARANCES OF RECTUM IN BACILLARY AND AMEBIC DYSENTERIES



PLATE XIV

Figs. 5 & 6. Sigmoidoscopic appearances of the rectum in Eastern Schistosomiasis (*S. japonicum*).
(Originals after P'an, Huang, Chiang, Lu, Hsu and Hsu, by permission).

cases of amœbiasis and 50 biopsies of patients with diffuse amœbic hepatitis. He failed to find *E. histolytica* in any of them. There was little anatomical evidence to justify the belief that diffuse amœbic hepatitis is a common finding in patients with intestinal amœbiasis. There is a growing belief that many cases of amœbic hepatitis may represent an allergic reaction to the presence of *E. histolytica*.

Thus in any ulcerative condition of the large intestine a similar reaction is liable to take place. The response of amœbic hepatitis to emetine may well be ascribed to its action upon the amœbic ulcers in the bowel (da Silva, 1954).

Complications.—Death may result from exhaustion, intestinal hæmorrhage, perforation, or liver abscess.

The most frequent complication of amœbic dysentery is liver abscess.

Perforation of the bowel may be sudden, or be preceded by intense local pain, which, when restricted to the right iliac fossa, may be mistaken for appendicitis. According to Howe this is a rare event, but is a very serious one. The bowel is usually so friable that at operation the sutures fail to hold. In subacute perforation pericolic abscess may be produced, especially in the descending or sigmoid colon. Intestinal obstruction from an amœbic granuloma (amœboma) has been recorded.

Amœbiasis may be superimposed upon bacillary dysentery, or *vice versa*. In Egypt, intestinal amœbiasis is often found associated with *Schistosoma mansoni*. Visceroptosis, distension or sacculation of the bowel, leading to intestinal stasis, may constitute distressing results of amœbic dysentery, but stricture of the rectum does not commonly ensue. In this situation it is funnel-shaped, some three inches from the anal margin; thus differing from the stricture of *lymphogranuloma venereum* or malignant disease. *Appendicitis* due to amœbic ulceration is not uncommon. Snapper has recorded a psoas abscess as the result of perforation of an amœbic ulcer of the cæcum.

Sequelæ.—Many sequelæ of intestinal amœbiasis have been described, often on insufficient evidence, and it is very difficult to prove direct association of different obscure clinical states with a past infection with *E. histolytica*. The Editor believes that certain intestinal conditions occur frequently as the aftermath of amœbiasis; such are appendicitis (not necessarily caused by amœbic ulceration), and mucous colitis. Chronic amœbiasis, besides producing chronic ill-health, very often contributes to introspection and neurasthenia.

Diagnosis.—It is safe to regard acutely developing tropical diarrhoea either as bacillary or amœbic dysentery, though clinical distinctions in the less acute manifestations are often unreliable. Assistance in diagnosis may be obtained from the more rapid onset, the febrile condition, and the rapid pulse in the bacillary disease. As a rule, the number of stools in bacillary dysentery is greater and their individual size less. The character of the stools should also be taken into account. Usually they are more offensive and contain more dark blood in amœbic dysentery. Occasionally, however, they may be tarry, suggesting duodenal ulceration.

Laboratory diagnosis should always be resorted to, having regard to

the experience of the observer and his ability to determine whether any amœba-like body discovered in the fæces is in fact *E. histolytica*, *E. coli*, or some large tissue cell, such as a macrophage (Plate XI). With practice this becomes comparatively easy. Entamœbæ may be absent in some portions of a stool; numerous in others. Several preparations must be searched, at first with the $\frac{3}{8}$ -in. lens, subsequently with the $\frac{1}{4}$ -in. Whenever possible, a portion of blood-stained mucus must be picked out for examination. The organisms may be difficult, or almost impossible, to detect in a specimen containing too much blood, and it is important that the specimen should be as fresh as possible. The discovery of an active amœba containing ingested red blood-corpuscles is generally sufficient to establish the identity of *E. histolytica*. In the more chronic and latent forms of the disease the characteristic cysts must be sought. It has often been claimed that daily purgation with salts promotes the discharge of amœbic cysts, but this is by no means certain. What may be a practical method of promoting the growth of *E. histolytica* in the bowel, has been put forward by Moody (1959). He has found that the corticosteroids do so in latent amœbiasis. Cholesterol acts as a growth factor and is promoted by cortisone. In his cases he gave hydrocortisone hemisuccinate by rectal retention enemata, oral prednisolone, 5 mgm. twice daily, and the amœbæ appeared in the stools in large numbers. Concentration methods of the detection of cysts are most useful and cultural methods less satisfactory. Entamœbæ and their cysts can at first be recognized under a low-power lens as "bright stars," of higher refractility than other cells, especially with the eosin contrast method whereby the background is stained pink whilst cysts stand out as clear refractile objects. Examination should not be considered as completely excluding an amœbic infection until the stool has been searched on each of seven consecutive days. Cultural methods may assist diagnosis in scanty infections.

In cases in which there is any doubt of the identity of the cysts, they may be stained by the rapid, or by the more prolonged iron-hæmatoxylin method. Kohn's staining method with chlorazol black gives the most vivid contrasts (see Appendix, p. 1094 and Plate XI). Mixing the fresh fæces with a solution of Weigert's iodine brings out nuclei and other characteristics; concentration methods may also be applied (see p. 1106), but they are time-consuming. As the protozoological scientific assessment of what constitutes *E. histolytica* is so confused the only sensible course for the clinician is to regard all forms, large or small, as potentially pathogenic. Minor features in the nucleus of the cyst of the non-pathogenic *E. hartmanni* have been described.

Charcot-Leyden crystals are commonly found in the fæces in amœbic dysentery, and their presence has been regarded as of diagnostic importance. The crystals vary very much in size, averaging $5-25\ \mu$; their typical shape resembles a whetstone, and they are soluble in warm water, strong mineral acids, and alcohol. They may also be found in preparations from amœbic ulcers, obtained through the sigmoidoscope (Plate XIII).

The Editor has pointed out the danger of attaching too much importance to Charcot-Leyden crystals as necessarily diagnostic of intestinal amœbiasis. He

has found them in malignant disease of the rectum, mucous colitis, coccidiosis (*Isospora hominis*), ulcerative colitis, and various helminthic infections (see p. 1106).

Complement fixation test (Craig). This test, which at present is of doubtful value, is carried out on the same lines as the Wassermann with an alcoholic extract of cultures of *E. histolytica* grown upon a modified Boeck-Drbohlav medium as antigen. A rich culture is obtained in association with *Trypanosoma cruzi*. Although it has been tested out in America on an extensive scale, the high proportion of false positives and negatives render it unreliable. Unfortunately the results in hepatic amœbiasis are no better (Wells, 1956).

Precipitin test.—Moan (1957) has devised a rapid precipitin test which, it is claimed, is reliable for clinical infections with *E. histolytica*. The test is, however, frequently negative in acute amœbic dysentery and also in asymptomatic carriers, but when tissue invasion has occurred, in a series other than acute amœbic dysentery, the test has given 85–100 per cent. positive. A figure of 95 per cent. positives was registered in one series of persons with positive stools who had recently been in contact with a severe outbreak, and 5 out of 5 positives in liver abscess cases. A drop of clear serum is mixed with a drop of special antigen and mixed on a Boerner rotator by hand at 120 r.p.m. for 4 mins. A specific precipitate is observed by the microscope as a basis of a positive test.

An *intradermal test* in amœbiasis is carried out with antigen prepared from cultures of different strains of *E. histolytica* and *E. moshkovskii* by Leal (1954).

These are washed, disintegrated and electrically shaken. After this extraction is carried out in a 1 : 10,000 solution of merthiolate in saline at 37° C. The antigen is sterilized by filtration through a Seitz filter. The injection is intradermal, in dose of 0.1 ml. and the result is read after 24 hours. In the tested individuals 36.3 per cent. had amœbic infection and 63.7 per cent. were controls. The test revealed a positive correlation between the infection detected microscopically and the reactions. The results obtained with *E. histolytica* agreed with those with *E. moshkovskii*.

The reaction appears as a form of erythema at the site of injection usually after three hours and measures 9–10 cm. in diameter.

Sigmoidoscopic examination.—Amœbic ulceration may extend into the rectal canal, so that sigmoidoscopic examination, conducted without an anæsthetic, usually affords valuable information. Commonly, small yellow ulcers with surrounding hyperæmia are seen, especially in the region of Houston's valves. It is often possible to demonstrate living entamœbæ in the scrapings, even when they cannot be found in the fæces. In contrast to chronic bacillary dysentery instrumentation is practically painless. Amœbic ulcerations may be touched or scraped without causing any painful sensation. The mucous membrane surrounding individual lesions shows absence of inflammation, preserves its normal pink colour, but it is usually more reticulated and folded than normal. Amœbic lesions are then seen in the crypts between the folds, either as small, yellow elevations the size of a pin's head, or as superficial snail-track ulcers with hæmorrhagic margins (Plate XIV). Large ulcers are rare. The unit of ulceration is a flat, shallow depression, with undermined edges, and of irregular diamond shape. Often the only signs of abnormality are small, flame-shaped hæmorrhages, in the centre of which entamœbæ may be demonstrated in scrapings obtained by means of a long-handled Volkmann's spoon passed through the sigmoidoscope (Fig. 85). A porcupine quill forms a convenient instrument for transferring

material from the spoon to the microscopic slide. American authorities describe an aspiration technique for obtaining material from the bowel for microscopic examination.

In the Editor's series of 585 cases of intestinal amœbiasis, 509 were diagnosed by microscopic examination of feces, in the remainder by demonstration of amœbæ in scrapings from amœbic ulcers. Out of 258 sigmoidoscopic examinations, amœbic lesions were demonstrated in 284.

In chronic, partially-healed amœbic dysentery, or even in symptomless cyst-passers, amœbic lesions may be distinguished as minute oval circular

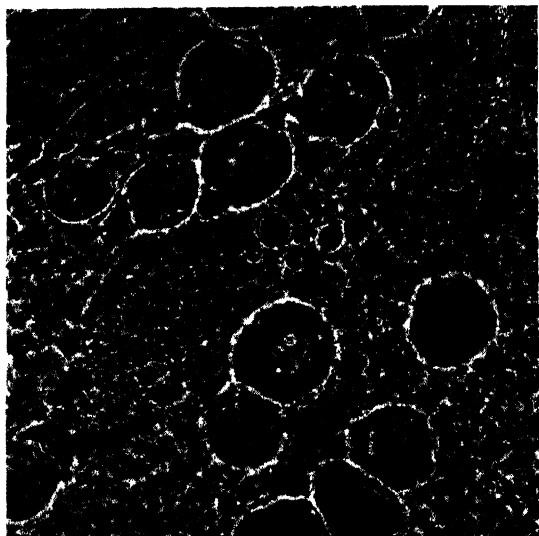


Fig. 85.—Amœbic dysentery, showing tissue-invasive *E. histolytica* in scrapings of ulcer obtained through the sigmoidoscope.

pits, or depressions ("pin-point craters"), irregularly disposed. They may be almost microscopic, requiring a magnifying eye-piece for their detection. The surface of the bowel may be peppered with them, giving the appearance of an aerial photograph of bomb craters. The term "pigskin appearance" has been appropriately applied by Cropper to minute scattered pits, resembling pinpricks on a plasticine surface, which persist even after treatment. Occasionally solitary amœbic ulcers, resembling carcinoma, are seen in the rectum, it may be twenty years or longer after the primary infection.

Proctoscopy affords an easily performed and less painful method of viewing the rectal mucosa. No special preparation is necessary. A tubular proctoscope about 6 in. long should be employed with a dental lamp, known as the straight illuminator lamp, as illuminant. The appearances are similar to those already described. Sometimes small granular areas and minute bleeding points can be seen. The Editor now employs this

as a routine method aided by biopsy material removed with a special long-handled Volkmann's spoon, with a stem of 16 ins. and a cup measuring 6 mm. in diameter. The material removed from the mucosa must be examined directly in a fresh state under the microscope. The cellular picture on microscopic examination gives valuable information. These observations have been confirmed by Jackman and Cooper.

X-rays in diagnosis.—Vallerino described, as indicative of amœbic lesions, filling defects in cæcum and ascending colon with deficient haustration of the bowel, seen after a barium meal, but not so easily after an opaque enema. X-ray diagnosis has been tried on an extended scale in London. Occasionally filling defects have been observed in the cæcum, but similar appearances are seen in other forms of dysentery and colitis. Sometimes when the cæcum is ulcerated the outline becomes ragged and triangular-shaped.

Differential Diagnosis.—Differential diagnosis has to be made from many other conditions in which blood and mucus are passed in the stools, in effect from all other forms of dysentery, colitis, or even other types of intestinal disease. From malignant disease of the bowel it deserves emphasis especially when an amœboma or amœbic granuloma is present (*see* p. 470). The X-ray appearances of amœbic hepatitis are very variable, as it is only in upward enlargements of the liver that elevation of the right dome of the diaphragm and restricted movement can be observed on screening. The paradoxical movement of the diaphragm is elicited by Müller's or Hitzenger's tests. The former—upward movement of the diaphragm on attempted respiration with closed glottis or nose and mouth—indicates damage to the power of contractility of the diaphragmatic muscles. The latter, produced by short respiration through the nose with mouth closed, is a modification of the former. This causes a short lasting negative intra-alveolar pressure due to respiratory expansion of the thorax with insufficient exchange of air. Amœbic hepatitis has to be distinguished from subtertian malaria, acute cholecystitis, gallstone colic, or empyema of gall-bladder. To those unfamiliar with the vagaries of amœbiasis the acute onset with pain may suggest rupture of a peptic ulcer. Differentiation of amœbic typhlitis from acute appendicitis, or appendix abscess, sometimes presents difficulties. For many reasons operation is undesirable in uncomplicated amœbiasis. Appendicitis is, however, a not infrequent sequel of amœbic dysentery. In amœbic typhlitis the X-ray appearances by barium enema assist. The cæcum is distorted and there are usually filling defects. Tenderness is diffuse, not localized directly over McBurney's point and the leucocyte response not so great as in appendicitis.

Treatment

I. Emetine.—There are four alkaloids of ipecacuanha but only one, emetine, has definite therapeutic properties. Emetine hydrochloride should be injected subcutaneously or intramuscularly. It is a toxic drug, especially to children and women, when given *intravenously*, or in excessive doses.

Dobell showed that emetine is lethal to amœbæ in culture, in a strength of one in five million. Nossina proved that this action is influenced by the acidity of the medium. It has a slight action in an acid medium, but the effect increases as the reaction approaches neutrality. The optimum is pH 6.8.

In large doses, greater than 1 grain a day, emetine is apt to produce toxic symptoms. It has a cumulative action and may lead to asthenia, cardiac

irregularity, emaciation, mental depression, and, in rare cases, to myositis or even neuritis. Emetine therapy is frequently followed by fine branny desquamation of the skin and atrophic brittleness and striation of the nails (Fig. 86). Emetine by injection exerts little action on the pre-cystic forms of *E. histolytica*.

The effective dosage of emetine seriously overlaps the toxic range. In special study by Brown in the Mayo Clinic toxic effects were recorded in 23 out of a series of 554 cases. Being a cytoplasmic poison emetine is especially toxic when given to patients with bacillary dysentery. Apart from its general action on the tissues, it has an especial affinity for the heart. This action has been shown by Epstein to be on the myocardium and the conducting fibres, but by electrocardiographic methods Heilig and others have shown that the cardiac effects have possibly been exaggerated.



Fig. 86.—Effect of emetine intoxication on the nails : increase of lunule, striation and brittleness. (Dr. T. Jackson.)

It is best to initiate treatment with a course of deep subcutaneous or intramuscular injections of emetine hydrochloride (1 gr. in 1 ml. of distilled water) daily for ten or twelve days. This does not suffice to eradicate the infection from the bowel. It should therefore be supplemented by a course of the *double iodide of emetine and bismuth* (emetine-bismuth iodide). Emetine injections are much more effective in *metastatic amœbic lesions* (hepatitis, etc.) than in intestinal amœbiasis. Disagreeable sequelæ may be avoided if the skin is pinched and the needle inserted *deep subcutaneously*.

II. Emetine-bismuth iodide contains 58 per cent. of iodine and 28 per cent. of emetine. In the intestine the insoluble salts of bismuth are converted into bismuth sulphide after passing the pylorus. It is indicated especially in chronic cases and in persistent passers of *E. histolytica* cysts. More usually known as E.B.I. it is an insoluble powder, from which the

emetine is set free by contact with the intestinal juices. It was formerly said not to be decomposed in acid solution (e.g. gastric juice), but this is incorrect. It passes through the intestinal canal unabsorbed, if compressed into a hard tablet (or *emplet*), or if coated with some insoluble substance, such as paraffin, vaseline, resin, keratin, or stearin. It is best made up in powder form in gelatin capsules (*Shipules*), or mixed with jam or syrup. The maximum individual dose for an adult is 8 gr. (0.2 gm.) per diem for ten to twelve consecutive days, but, if not well tolerated, smaller doses suffice. For delicate individuals and women the dose should commence with 1 gr. and be gradually increased. This drug is more easily tolerated in temperate climates than in the tropics.

If gelatin capsules have been kept for some time they tend to harden and become insoluble. They should therefore be pricked with a pin before being administered. Sugar-coated preparations are also quite satisfactory.

It is important to observe certain precautions in giving this drug. When given at 10 p.m., the last solid food should be taken at 4.30 p.m.; the patient should remain at rest; he should endeavour to go to sleep, and any saliva should be wiped from the mouth.

Vomiting and diarrhoea may occur in the earlier part of the course, and are to be viewed as an indication that the drug is being absorbed. It is necessary for the patient to remain in bed and take a liquid or milk diet with eggs and toast.

Excessive vomiting and nausea may be mitigated by 10-15 min. of *tinct. opii* given half an hour previously, or, in some patients, by nepenthe, luminal, allonal, or chloretone. Most patients lose about 5 lb. in weight while under treatment. The condition of the heart and pulse should be noted daily, but treatment should not be discontinued unless depression becomes severe. Blood pressure is usually reduced.

For relapsing cases it was formerly considered necessary to give more than one course of E.B.I. and some were thought to be due to amebæ which had become resistant. Too much reliance should not be laid on isolated stool examinations, on account of the vicarious appearances of the cysts, but it is advisable to re-examine faeces microscopically at the end of six weeks. The results of treatment are much better controlled by periodic sigmoidoscopic, or proctoscopic, examinations. For some considerable time after disappearance of active lesions, small pits or depressions of the mucous membrane may be seen.

III. Iodine-oxyquinoline-sulphonic-acid preparations (*Quinoxyl*)—Sodium-iodoxy-quinoline sulphate is also known as *Chiniofon* (B.P.), *Yatren* (Bayer), *Quiniosulphan* (May & Baker), *Anayodin* (U.S.A.) and *Dysentulin* (German). It is a mixture of four parts of 7-iodo-8-hydroxy-quinoline-5-sulphonic acid, containing not less than 26.5 per cent. combined iodine, and one part of sodium bicarbonate. There is some chemical reaction, so that the preparation may contain a small amount of sodium hydroxyquinoline sulphonate, in addition to sodium bicarbonate and iodohydroxy-quinoline sulphonic acid. In solution 100 parts of quinoxyl yield approximately 85 parts of iodohydroxyquinoline sulphonate. Quinoxyl can be given either by the mouth or by retention enema. By the former route the maximum daily dose is 1 gm. (15 gr.) in powder form, in capsules, or keratin-coated pills, for ten days. After an interval

of one week this course should be repeated. The drug is excreted in the urine, and can be recognized by the oxyquinoline test (green colour with perchloride of iron).

Quinoxyl may be given as rectal injections (retention enema), as well as by the mouth. The bowel must first be washed out and cleared of mucus by an enema (1 pint) of 2 per cent. sodium bicarbonate at 8 a.m. One hour later 227 ml. (8 oz.) of a 2.5 per cent. solution of quinoxyl, in warm water, is introduced through a stout rectal tube. The patient should be encouraged to retain it as long as possible, from 4 to 10 hours. The solution is then returned as a greenish liquid containing mucus and debris derived from the bowel. The course of rectal injections is continued for ten days. The course may be repeated two or three times with a week's interval between each. Dieting and rest in bed are absolutely necessary.

IV. Combined or synergistic treatment.—This method of treatment gives permanent results. It is assumed that E.B.I. acts on the amœbic lesions in the upper portion of the large intestine, quinoxyl on ulcers and lesions situated in the lower portion. It is necessary that the patient should be *at rest* and *in bed* the whole of the ten days of this treatment. Due attention must be paid to the dietary. It is not necessary to give more than a total of 90 gr. of F.B.I. and the maximum individual dose should not exceed 3 gr.

SCHEME OF DIETARY AND COMBINED TREATMENT FOR INTESTINAL AMŒBIASIS

- 7 a.m., pot of tea and 2 oz. milk.
- 7.30 a.m., one egg, buttered toast, cup of tea and 2 oz. milk.
- 8 a.m., sodium-bicarbonate enema, 2 per cent., 1 pint.
- 8.30 a.m., quinoxyl $2\frac{1}{2}$ per cent. by rectum (8 oz.).
- 9 a.m., 8 oz. milk.
- 10.30 a.m., juice of an orange, glucose $\frac{1}{2}$ oz.
- 12 noon, liver soup, chicken or fish, toast, butter, custard or milk jelly, baked apple.
- 4 p.m., boiled egg, toast, butter, juice of one orange and $\frac{1}{2}$ oz. glucose, grapes or ripe banana, sponge fingers.
- 5 p.m., quinoxyl enema voided. (Further experience has shown that 6 rectal retention enemata suffice.)
- 6 p.m., 8 oz. milk; bath.
- 9.30 p.m., sedative (luminal gr. 1; tuinal or secconal gr. $1\frac{1}{2}$).
- 10 p.m., E.B.I. (gr. 3).
- 10.30 p.m., sleep.

During combined treatment the patient should be nursed in bed and should be allowed to get up for his bath. He may be allowed to use a night commode for stools and for voiding the residue of the quinoxyl enema. On the first night E.B.I., gr. 1, is given; subsequently, gr. 2 and gr. 3.

Other methods of treatment.—*Stovarsol* (*Acetarsol*), an arsenical preparation (3-acetyl-amino-4-hydroxyphenyl-arsonic acid), containing 27.2 per cent. of arsenic, has been advocated, mainly in France, as an amœbicide, and has been widely used in the treatment of amœbic dysentery in combination with other drugs. It has a feeble amœbicidal action, but stimulating properties. Its special use is in the after-cure of amœbiasis. It is dispensed in 4-gr. tablets, and the maximum dose is two daily for one week to ten days.

Carbarsone has been much used in America and is given in the same manner as *stovarsol*, and has apparently the same therapeutic properties and the same indications for chronic amoebiasis and for cyst passers. Most American authorities advise a dose of 0.25 gm. twice daily in capsules (pulvules) for ten days. Both *stovarsol* and *carbarsone* may be administered *per rectum* in the form of retention enemata of 2 gm. in 220 ml. of warm 2 per cent. sodium bicarbonate solution.

Milibis (*Wia*) (Winthrop) is a bismuth derivative of *p*-N-glycolylarsanilic acid, and contains 15 per cent. arsenic in pentavalent form and 41.88 per cent. bismuth. It has an action rather similar to that of *carbarsone*, but it is, however, less soluble and has acquired a very considerable reputation in the treatment of chronic amoebiasis especially in emetine-resistant cases. The tablets, of 250 mgm. each, are given two to three times daily for seven days.

Vioform, or *entérovioform* (iodochlorhydroxyquinoline), is somewhat similar to iodoform and contains 37.5 per cent. of iodine. It is administered by the mouth in gelatin capsules each containing 0.25 gm. (4 gr.) of the powder, three times daily, for ten days. In chronic cases it may be injected for ten days as retention enemata, consisting of 150–200 ml. of warm water in which 2 tablets have been dissolved.

Diodoquin, *Diiodohydroxyquinoline*, *Dihaloquin*, *Savorquine*, or *Embequin* contains 63.9 per cent. iodine. Its action is similar to that of *vioform* and has proved itself a valuable drug. It is non-toxic, well tolerated and useful for mass ambulatory treatment of chronic amoebiasis. It has very definite amoebicidal action, but is not satisfactory in the active stages of amoebiasis, though of great assistance in clearing up *symptomless* cyst carriers. In a few cases it causes pruritus ani. Tablets of 3.2 gr. are given by the mouth. The customary dose is 8 tablets daily for 15 days.

Two new amoebicides have been introduced in *Entamide* and *Mantomide* (see pp. 872, 874) and are now under trial. Laboratory tests are encouraging. Woolfe (1957) gives the following figures for cultures of *E. histolytica*:

Emetine hydrochloride active at	1: 500,000.
Entamide hydrochloride active at	1: 10,000,000.
Mantomide hydrochloride active at	1: 1,000,000.

Antibiotics in Treatment of Amoebic Dysentery.—*Aureomycin* has been shown to exert an action upon *E. histolytica* in culture (see p. 927) but most authorities (Anderson, Bradin and Hansen) suggested that *aureomycin* is not directly amoebicidal when tested out on 52 African cases, five of which were of exceptional severity. The first effect is to lower the number of stools and to reduce the bacterial flora. The dose employed is 0.25 gm. four times daily (1 gm.) for 15 days. Disappearance of amoebæ was not only rapid, but dramatic. The effect was, however, temporary, because the relapse rate was high within two weeks of cessation. Armstrong, Wilmot and Elsdon-Dew (1950) in Africans gave 0.25 gm. four times daily at six-hour intervals for 15 days. Daily sigmoidoscopy showed remarkably rapid healing. Disappearance of amoebæ was equally rapid, but relapse rate was high.

Terramycin (Oxytetracycline).—This antibiotic has been introduced into the treatment of amoebiasis and has received some favourable comment. Sanchez and colleagues in Mexico found that 40 mgm. per kg. for 4 days resulted in a satisfactory cure. Most and van Assendelft (1951) have used it on a much more extended scale with doses of 1 gm. for children and 2 gm. for adults daily for from 5 to 10 days. Out of 37 persons treated with a full course all, but one, remained free from parasitic relapse.

General observations on antibiotics.—It was thought that the main action of antibiotics was on organisms other than the amoebæ, but now there is evidence

that aureomycin and terramycin have some direct anti-amœbic effect, but against this it has been shown that the former drug has some effect on these organisms in amœbic abscess or in amœbic hepatitis. One great feature of the antibiotic treatment is the rapidity with which the lesions heal and the amœbæ disappear. With aureomycin 1 grm. daily in divided doses, on the tenth day 67 per cent. of cases had been cleared of their ulcers and 98 per cent. of their amœbæ; with terramycin in the same doses, 84 per cent. and 94 per cent., respectively. Procaine penicillin and succinyl sulphathiazole appear to have a synergistic effect and were much more successful than in combination with other sulphonamides. With antibiotics early relapses after 4-8 weeks are usual.

Frye, in Korea (1953), has summarized his experience as follows on the immediate results of antibiotic treatment. Stools were examined daily and the results checked by frequent sigmoidoscopies.

	NUMBER TREATED	SUCCESSES	FAILURES
Terramycin ..	40	39	1=2.5%
Aureomycin	41	29	12=29.3%
Chloramphenicol	39	21	18=46.2%

The careful and extensive observations of Woodruff (1956), carried out with controls under comparable conditions, have led to the conviction that, dramatic as the action of antibiotics on *E. histolytica* appears to be, the results are not lasting, unless combined with the older methods of treatment with emetine and E.B.I. Therefore, other things being equal, the latter should be relied upon.

Treatment of hepatitis.—During the course of amœbic dysentery, and for months afterwards, the liver must receive careful attention. It may not be possible to prevent abscess formation; but if pain persists, an attempt to avert this grave complication may be made by giving repeated doses of emetine subcutaneously, saline aperients, rest, low diet, fomentations and similar measures. Emetine acts much more rapidly and specifically in hepatitis than in amœbic infection of the bowel, and in some cases aspiration of the liver (hepatic phlebectomy) has a wonderful effect. Usually a total of 6 gr. of emetine suffices to overcome the more active symptoms and should be followed by chloroquine (see p. 494).

Perforation of amœbic ulcer.—To avoid fatal peritonitis, diagnosis of perforation of the large bowel should be made as soon as possible. The difficulties have been emphasized by James during the recent war in five cases of perforation of the cæcum and colon. The time factor is of supreme importance. Fæcal fistulæ are apt to form. When perforation occurs in a fixed portion of the colon it can be closed and covered with omentum. The difficulty of making silk sutures hold is emphasized.

Barker (1959) has reported upon the treatment of colonic perforation in Durban amœbiasis where, out of 2-3,000 admitted to hospital there, 20-30 had colonic perforations. Usually toxæmia with dehydration and electrolytic imbalance and paralytic ileus are concurrent. Presence of free fluid in the peritoneum and X-ray evidence of free intraperitoneal gas, is proved by lateral radiography in the supine position. *In these cases surgical intervention is both useless and dangerous.* Gratifying results are obtained with control of dehydration and electrolytic imbalance, emetine injections and intravenous oxytetracycline. Surgical measures should be reserved for other forms of perforation in less severe amœbic dysentery, such as amœboma and pericolic abscess.

Amœbic appendicitis and typhlitis.—If operation is undertaken, the minimum and most gentle handling of the bowel is necessary. It must first be determined whether the condition of the cæcum is secondary to that of the appendix or *vice versa*.

Diet.—A suitable diet in the convalescent treatment of amœbic dysentery is important. Alcohol, unless taken in small quantities, certainly pre-disposes to relapse. The following diet is advocated for four weeks after active treatment:

Permitted.—Porridge; eggs; filleted or fried fish—haddock, plaice, cod, sole or whiting; toast or rusks; milk puddings—rice, sago, semolina, ground rice; spinach or young peas, vegetable marrow, cauliflower; plain cakes; fruit jellies; stewed pears or peaches; baked apples; bananas, grapes; tripe, brains, sweetbreads; chicken; rabbit; game.

Not permitted.—Cheese; new bread; potatoes; fats; suet puddings; rich cakes with raisins or spices; pastry; pickles.

Meat.—Red meat, i.e., mutton or beef, can be permitted once daily.

Surgical measures must be reserved for complications of amœbiasis, such as pericolic abscess. Dunlop (1946) has written a vivid description of the appalling severity of amœbic bowel lesions in Japanese prison camps. The surgical cases fell into two groups. The acute cases, in which the principal difficulty was relief of pain, tenesmus and wasting were much benefited by appendicostomy and cæcostomy. Chronic cases with grossly damaged colons, which had failed to respond to anti-amœbic treatment, were subjected to ileostomy and the results were dramatic in 14 cases.

Prophylaxis of amœbiasis is practically the same as for bacillary dysentery, and depends upon efficient sanitation, measures directed against the housefly, and avoidance of unboiled water, raw vegetables, or other foods which may have been contaminated by human faeces. As cysts of *E. histolytica* can only survive in a moist medium, there is a considerable amount of evidence, experimental and epidemiological, that amœbic infection is usually waterborne. The problem of dealing with human carriers of *E. histolytica* cysts is a constant difficulty. It is not likely to arise in countries equipped with a proper system of sanitation, but in no case ought a cyst-carrier to be employed as cook or mess orderly, or handle water supplies.

Water contaminated by *E. histolytica* cysts should be treated as follows:

- (1) Heavy dose of aluminium sulphate at the rate of 6–10 gr. per gallon.
- (2) Allowed to settle for 1 hour.
- (3) Filtered at a rate not to exceed 6 gallons per sq. foot of filter surface per minute.
- (4) Finally chlorinated.

For small-scale water supplies, the greatest amount of protection is provided by filtration through diatomaceous silica after previous sedimentation.

COMPLICATIONS OF AMŒBIASIS

1. HEPATIC ABSCESS (LIVER ABSCESS; HEPATIC AMŒBIASIS)

Geographical distribution.—Liver abscess of the type known as tropical abscess, for the most part a disease of warm climates, corresponds

in its distribution with amœbiasis. While the entamœba is the principal element in its production, its incidence depends probably on special susceptibility of the European to this complication.

Ætiology. *Relation to amœbic dysentery.*—There can be no question of the existence of an intimate relationship between amœbic dysentery and liver abscess. Many well-authenticated statistics, as well as everyday experience, attest this. In 3,680 dysentery autopsies made in various tropical countries, and collated by Woodward, 779 (21 per cent.) revealed abscesses of the liver. Extensive amœbic ulceration may exist without exciting any subjective symptoms. Moreover, many patients suffering from liver abscess forget, or fail to mention, a previous dysenteric attack, or may mislead the physician by describing such an attack as "diarrhœa," so that the relationship is much more intimate than even statistics indicate. In the great majority of cases dysentery antedates the abscess, it may be by as long as twenty years.



Fig. 87.—Structure of milillary amœbic hepatic abscess containing *E. histolytica*. (P. H. M.-B. (Original case).)

Race, sex, and climate.—Though common in Europeans in the tropics, liver abscess is proportionately rare among natives. Thus, in the native army of India, the proportion of deaths from liver abscess to the total mortality in 1894 was only 0.6 per cent., whereas in the British army it was 7.4 per cent. Man for man, the relative liability of the European and the Indian soldier was as 95.2 to 4.8. This disproportion holds in spite of the fact that a larger proportion of Indians are infected with *E. histolytica*.

It is well known that European women in the tropics, though nearly as subject to dysentery as European men, rarely suffer from liver abscess, and children hardly ever. It is most common between the ages of 20 and 40, though there are records of amœbic abscesses of the liver in Egyptian children of three months of age and of others in India of ten. In Durban, where amœbiasis is widespread amongst the Zulus, amœbic hepatitis and amœbic abscess frequently occur in small children of one or two years of age. This incidence is quite exceptional.

Pathology.—It may be inferred from the symptoms that in the early stages of suppurative hepatitis there is general congestion and enlargement of the liver; in some instances this condition may be more or less confined to one lobe or even part of it. Later, as shown especially by observations on cases that have died from the attendant dysentery, one or more greyish, ill-defined, circular patches, $\frac{1}{2}$ –1 in. or therabouts in diameter, are formed (Fig. 87). A drop or two of a reddish, gummy pus may be expressed from these necrotic patches. Still later, the centres liquefy, and distinct but ragged abscess cavities are formed. An abscess thus commenced extends partly by breaking down of liver parenchyma; partly by more massive necrosis of portions of its wall; partly by the formation of additional foci of softening in the neighbourhood, and subsequent breaking down of the intervening septa. As the abscess enlarges, so the zone of necrotic tissue becomes narrower. The character of the contained pus also changes during the evolution of the abscess; it frequently becomes secondarily infected with streptococci and other organisms, when it assumes a brownish or greenish colour

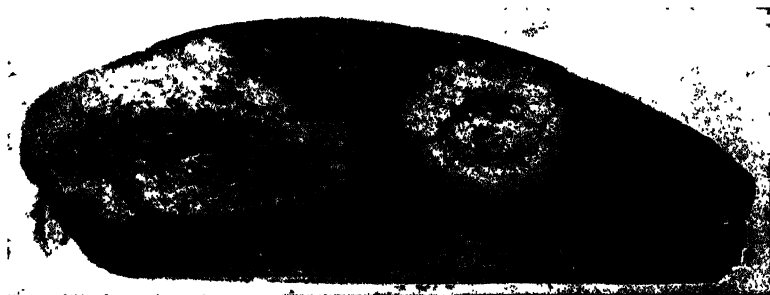


Fig. 88.—Multiple liver-abscesses from a case of acute amœbic dysentery, showing characteristic structure and zone of acute hyperæmia. Quarter nat. size.

Number, size, and situation of abscesses.—Liver abscess may be single or multiple. If multiple, there may be two, three, or many. When single, the abscess sometimes attains a great size. Frequently it is as large as a coco-nut, or even larger; the entire liver even, with the exception of a narrow zone of hepatic tissue, having been converted into a huge abscess sac. When multiple, the individual abscesses are generally smaller, ranging from the size of a filbert to that of an orange (Fig. 88).

As might be expected from considerations of the relative size of the parts, single abscess is much more common in the right than in the left smaller lobe. The upper part of the right lobe might be termed the seat of election. Compensatory hypertrophy of the left lobe is commonly produced whenever there is great destruction of the right.

Adhesions to surrounding organs are frequently, though not invariably, formed as the abscess approaches the surface of the liver. In this way the danger of intraperitoneal extravasation is usually averted.

Intestinal ulceration usually co-exists; it may be very extensive, or confined to a few small punched-out ulcers, generally in the neighbourhood of the cæcum. Or, again, there may be no visible lesions of the mucous surface.

Pulmonary inflammation and abscess from escape of liver pus into the lungs are sometimes discovered *post mortem*. Generally the pulmonary abscess communicates with the mother abscess in the liver by a small opening in the diaphragm, the pleural sac being shut off by adhesions. (Plate XVI.)

Liver pus.—The naked-eye appearance of liver pus is peculiar, almost characteristic. When newly evacuated, it is usually chocolate-coloured, streaked, or mixed, with larger or smaller clots or streaks of blood, and here and there with streaks of clear mucoid yellowish material. It is so viscid that it will hardly soak into the dressings, lies on the surface of the gauze like treacle on bread, spreading out between the skin and the dressing, and finding its way past the edge of the latter rather than penetrating it. When quite fresh, here and there, little islands of what may be described as laudable pus may be made out in

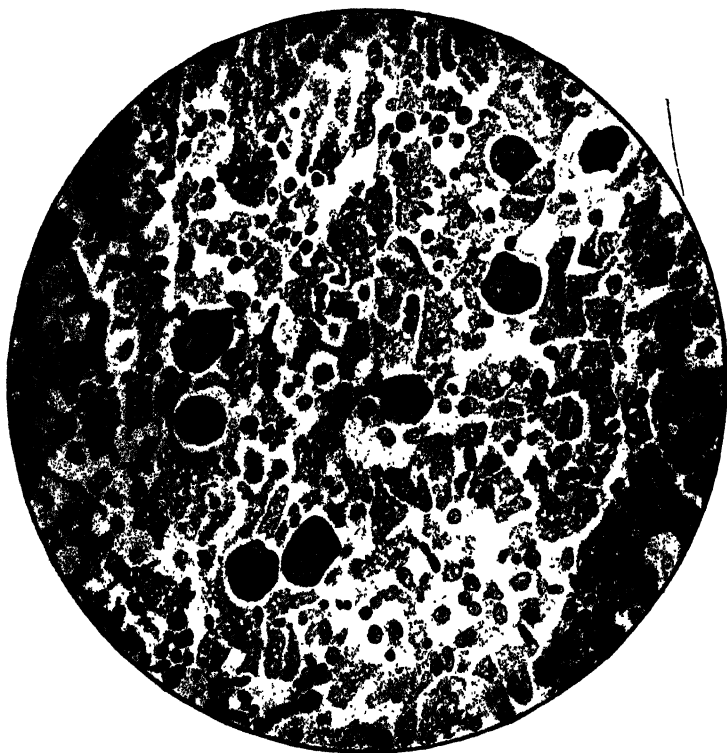


Fig. 89.—Microscopical section of liver abscess, showing *Entamoeba histolytica* at margin of abscess cavity surrounded by necrotic liver cells.

the brown mass. Occasionally, also, from admixture of bile, the abscess contents are green-tinged; they are rarely offensive, unless the abscess lies near the colon. Under the microscope many blood-corpuscles are seen, besides much broken-down liver tissue, large granular pigmented spherical cells, lecithin plaques, leucocytes, débris, oil globules, hæmatoidin, occasionally cholesterin, Charcot-Leyden crystals and sometimes entamœbæ. Cysts of *E. histolytica* are never found.

Entamœbæ and other organisms.—In Egypt, India, and elsewhere entamœbæ may be detected in half the cases. Usually they cannot be found in fresh liver pus, either aspirated or escaping during operation, but they appear, often in great

profusion, four or five days later in discharges from the drainage-tube in strings of eight to ten. Unless the patient is treated with emetine, the amœbæ may persist in the discharge until the abscess has healed and occasionally they can be grown on Drbohlav's medium, but the longer the abscess has persisted the larger its size, and the more difficult it is to find amœbæ (Fig. 89). The pus is bacteriologically sterile, but occasionally may become secondarily infected by *Bact. coli*, hæmolytic staphylococci, streptococci and *Salmonella enteritidis*, in which case the entamœbæ in the liver pus are destroyed. There is some evidence that in the majority the secondary bacterial infection is derived from the bowel, more rarely from the lungs.

Encystment.—In rare instances liver abscess pus, instead of being chocolate-coloured and viscid, is yellow and creamy, particularly when the abscess becomes encysted. The walls are thick, smooth and fibrous. In the course of time the contents become cheesy, and ultimately cretified until the cyst shrivels up and contracts (see Plate XV). Calcified abscesses are occasionally found by radiography, and do not give rise to symptoms. They have to be differentiated from calcified hydatid cysts and sometimes also from calcified suprarenals.

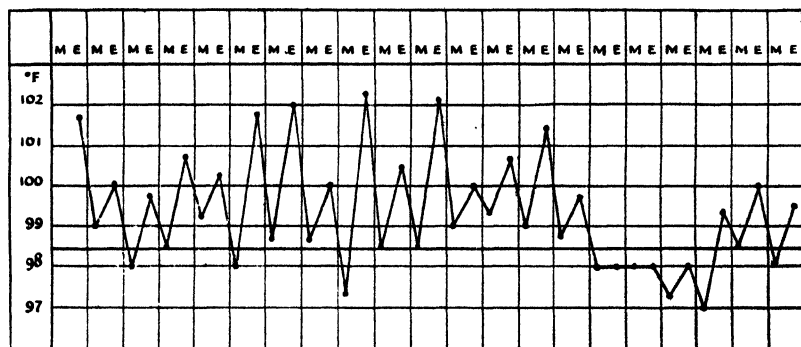


Chart 23.—Amœbic abscess of liver.

The genesis of liver abscess.—Amœbic abscess of the liver appears to be the result of portal embolism from amœbic ulcers in the bowel. This focus is usually in the right sector of the abdomen, either in the cæcum or ascending colon; this fact, therefore, accounts for the common situation of such an abscess in the right hepatic lobe. Direct infection of the anterior surface of the liver may possibly take place from an amœbic ulcer in the hepatic flexure, *via* the peritoneum, but there is no evidence to show that this constitutes the usual method. In *amœbic hepatitis*, which is probably the precursor of amœbic abscess, there appears to be a massive amœbic portal infection. Probably the great majority of the organisms are destroyed by resulting tissue-reaction but survivors multiply and cause necrosis of the surrounding liver cells and thus constitute the starting point of a liver abscess. Most authorities believe that allergic reactions play a prominent part. Cytolysis is brought about by the rapidly multiplying amœbæ; but ultimately the amœbæ themselves are destroyed by the products of their own activity. As originally pointed out by Councilman and Lafleur, the primary lesion is central necrosis of the liver lobule, a prelude to subsequent abscess formation.

detected from the angle of the scapula to the costal margin. It may be further observed that the upper line of dullness is arched, and is altered by changes in position, when the patient lies on his left side or when he stands up. Deep inspiration may give rise to acute pain, and sometimes one or two tender points may be discovered in the lower intercostal spaces. The spleen is not enlarged. On auscultation, pleuritic rubs may be detected at the base of the right lung, or signs of compression, such as inspiratory crepitations, decreased breath-sounds, or diminution of vocal fremitus may be noted at the base of the right lung (Fig. 90). Pain is usually relieved by lying on the affected side (Fig. 91).

In abscess of the left lobe a tumour of variable outline, sometimes resembling in shape and position an enlarged spleen, may be felt in the epi- or hypogastrium. Usually there is some compression involvement of the base of the left lung, but it must be remembered that such a tumour may arise from compensatory hypertrophy of the left lobe.

As the case progresses, so the patient becomes more emaciated; hectic fevers with drenching nocturnal sweats continue; liver dullness and pain increase; or general enlargement may subside, and percussion reveal a local bulging in an upward or downward direction. If the abscess which has now formed is not relieved, the patient may die worn out after months of illness; or the abscess, having attained great dimensions, may burst into the right lung or pleura, or even elsewhere, and be discharged with either recovery, or death from continued hectic fever and exhaustion, or from some intercurrent complication. (Plate XVI.)

The blood shows a well-marked leucocytosis of 15,000–35,000, though in some rare cases there may be no appreciable rise. The mean average of the differential count in the Editor's series of cases is 70·8 per cent. polymorphonuclears; 22·2 per cent. lymphocytes; 6 per cent. large mononuclears; and 1 per cent. eosinophils¹. With liver abscess of long standing there is usually severe secondary anaemia, and occasionally the blood changes may assume features of the pernicious type.

Great variety in the urgency of symptoms.—Although the foregoing is a fairly common history in liver abscess, there are many instances in which the initial symptoms are much more urgent and the disease



Fig. 90.—Clinical picture of liver abscess, showing enlargement of liver and bulging of chest wall. (42 ozs. of pus aspirated.) (Philip Manson-Bahr.)

¹ Occasionally an eosinophilia has been recorded in association with liver abscess.

progresses much more rapidly. In other instances subjective symptoms are almost entirely absent, or so subdued that the true nature of the case may be entirely misapprehended until the abscess bursts through the lung or bowel, or a fluctuating tumour appears in the neighbourhood of the liver ; or, perhaps, until the unsuspected abscess is discovered on the post-mortem table.

Sometimes the initial fever is high, and persists for a considerable time, but later it usually becomes distinctly quotidian and intermittent ; some times temperatures of 103° and 104° F. may be recorded. There is not one single cardinal sign which may not be absent in hepatic abscess ; thus, large collections of pus have been noted unaccompanied by fever. Marked rigors are rare but, when present, indicate threatened rupture through the diaphragm or into some viscus. Sweating accompanying the pyrexia usually takes place about the head and neck. Enlarged cervical and axillary glands on the affected side may sometimes be noted, while rheumatic-like pains in, or swellings around joints, and clubbing of fingers have been described. Pain of some description is rarely absent. Usually, a sense of fullness and weight in the region of the liver, or referred to the infrascapular region, is complained of ; stabbing and stitch-like pains may be increased by pressure, and especially by deep inspiration or coughing. Localized painful areas usually occur below the costal margin, and indicate that the abscess is pointing in that direction. Pain on swallowing, when the bolus traverses the lower end of the œsophagus, has been recorded. Pain on firm pressure with the finger-tips in an intercostal space, and over a limited area, is a common and valuable localizing sign. Shoulder pain, in about one-sixth of the cases, may be the only symptom and may be noted before the advent of fever. The sudden appearance of pain in the right shoulder is an early sign of diaphragmatic penetration. There is one point that should be remembered in what is known as Guéneau de Mussy's point which is found in diaphragmatic pleurisy and serves to differentiate it from hepatic amœbiasis. This point is exceedingly painful on pressure on the line of the left border of the sternum at the level of the tenth rib.

Attention may also be drawn to the respiratory symptoms ; a painful cough, possibly due to reflex irritation of the diaphragm, may be prominent, while the respiration may be rapid and shallow. The patient usually lies on his back, inclining slightly to the affected side ; if the abscess is on the right, lying on the *left* side becomes distressing owing to adhesions, or possibly to pressure on the heart.

The tongue is generally furred, the digestion disturbed ; flatulence and diarrhœa are frequent. There may, but infrequently, be concurrent amœbic dysentery with blood and mucus in the stools.

The heart may be displaced laterally or upwards by pressure of a large abscess. Tachycardia and cardiac irregularities may result from toxic absorption or from pressure.

Rigidity of the upper part of the right rectus muscle may be noted if the abscess is situated in the vicinity of the gall-bladder. Percussion, besides eliciting tenderness and causing pain, may convey to the examiner a sensation of *ballotement* as of percussing a thick-walled elastic bag

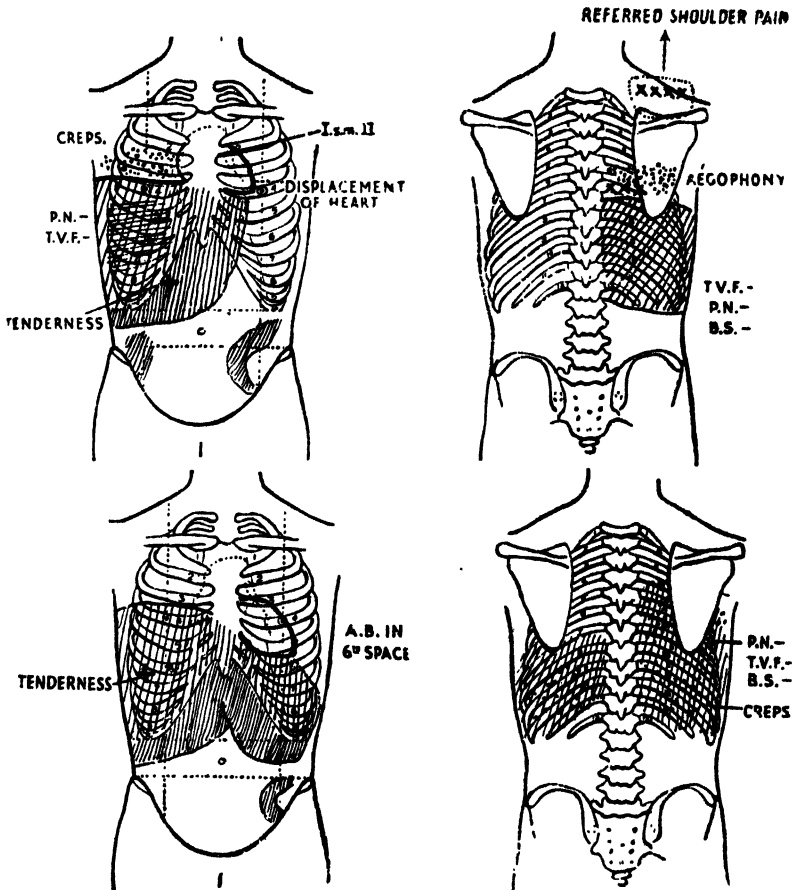


Fig. 91.—Physical signs of liver abscess.

Above—Of right lobe of liver, cured by aspiration with Potain's aspirator.

Leucocytes, 9,000; *E. histolytica* cysts in faeces. I.s.m. II, basal systolic murmur; P.N.—, percussion note diminished; T.V.F.—, tactile vocal fremitus diminished; B.S.—, breath-sounds absent; CREPS., crepitations.

Below—With hypertrophy of the left lobe, cured by aspiration of 65 ounces of sterile pus.

Leucocytes, 12,000; *E. histolytica* cysts in faeces. A.B. apex-beat; P.N.—, percussion note diminished; T.V.F.—, tactile vocal fremitus diminished; B.S.—, breath-sounds absent; CREPS., crepitations.

filled with air. The right upper superficial reflex may be diminished or absent.

Swellings in the epi- or hypogastrium closely simulate intra-abdominal tumours, and in apyrexial cases of hepatic abscess their nature may not be suspected until they have been aspirated. There may be varicosity of the epigastric veins. Local *œdema* over one or more intercostal spaces

is sometimes apparent ; local *bulging* usually indicates the site at which the abscess is pointing (Fig. 91).

Friction rubs, pleuritic or peritoneal, may sometimes be found ; while pneumonic signs at the base of the right lung indicate contiguity of the abscess to the diaphragm. Oedema of the feet occurs in advanced cases.

The urine may contain albumin as the result of chronic pus-absorption. When considerable destruction of hepatic substance has taken place, the amount of urea is diminished and that of ammonia increased.

Jaundice is not by any means common ; when deep it may be caused by pressure of an abscess of the caudate lobe on the common bile duct. Toxic jaundice is sometimes met in secondarily infected abscesses, or may be due to coexisting infective hepatitis. Quite commonly, however, there is a subicteric tint with slight yellow tingeing of the conjunctivæ.

The abscess may rupture into any contiguous organ, thereby producing spontaneous cure ; generally it ruptures into the lung or pleura. When into the *lung*, the abscess contents may be suddenly coughed up in mouthfuls of frothy pus and blood ; but usually this process is much more gradual and a few drachms are coughed up at a time, but in favourable cases the amount of expectoration gradually diminishes. Amoebic abscess of the lung—resulting from trans-diaphragmatic rupture—is apt to be mistaken for pulmonary tuberculosis. Amoebæ are only exceptionally found in the expectorated pus, but usually striated muscular fibres from the diaphragm may be recognized.

Expectorated liver-pus is usually characteristic, being chocolate-brown and particularly viscid.

Arrest of the discharge may not necessarily indicate recovery though cessation of the cough may be followed by rise of temperature and re-appearance of night-sweats. Alternate emptying and refilling of the abscess cavity may recur many times before final recovery. In some cases expectoration never ceases, and is accompanied by other signs of pulmonary absorption, such as respiratory distress and clubbed fingers. Sudden rupture is often accompanied by the passage of melænic stools.

Rupture into the *pleura* may lead to pleural effusions, which may simulate empyema. Aspiration of these cases may yield clear yellow and highly albuminous pleuritic fluid. Pneumothorax may sometimes ensue.

Hepatic abscess may rupture into the *stomach*, causing vomiting of pus ; into the *bowel*, causing diarrhoea and discharge of pus in the faeces ; or, with fatal results, into the *pericardium* or *peritoneum*. Pericarditis, from close contact with intrahepatic suppuration, has been recorded. A case reported by Hartz (1950) arose from the sudden perforation of a left hepatic abscess into the pericardial cavity.

Rupture into the gall-bladder, bile-ducts, hepatic veins, portal veins, inferior vena cava and pelvis of the right kidney have also been reported.

Finally, spontaneous rupture may take place through the abdominal wall, and the abscess, by tracking along the round ligament, may empty itself. The surrounding skin may thus become infected with amoebæ.

Mortality.—Formerly the case-mortality was high, 50–80 per cent.

but at the present day, chloroquine and emetine, recognition of the intimate connection of liver abscess with amœbic dysentery, and improved methods for the evacuation of pus, have brought the mortality-rate to practically nothing.

Diagnosis—The most common mistakes in diagnosis are: (1) Failure to recognize the presence of disease of any description, even when an enormous abscess occupies the liver. (2) Misinterpretation of the significance and nature of a basal pneumonia—a condition often accompanying suppurative hepatitis. (3) Attributing the fever symptomatic of liver abscess to malaria. (4) Mistaking other diseases for abscess of the liver, and *vice versa*—for example, non-suppurative hepatitis, such as that attending subtertian malaria; suppurative hepatitis before the formation of abscess; syphilitic disease of the liver—softening gummata which are often attended by hectic fever—; bronchogenic carcinoma; bronchiectasis; atypical pneumonia; tuberculosis; pylephlebitis; suppurating hydatid; suppurating actinomycosis; gall-stones and inflammation of the gall-bladder; subphrenic abscess due to ruptured gastric or duodenal ulcer, or appendix abscess; abscess of the abdominal or thoracic wall; pleurisy; encysted empyema; pyelitis of the right kidney; schistosomiasis; scurvy and similar blood-diseases associated with hepatic enlargement; ulcerative endocarditis; kala-azar; undulant fever; trypanosomiasis, tuberculosis, and malignant disease. Any of these may be attended with fever of a hectic type, increased area of hepatic percussion dullness, and pain in or about the liver.

Differential diagnosis from suppurative cholecystitis without the aid of a "shadowcol" examination may be particularly difficult.

Suprahepatic abscess is not synonymous with "subdiaphragmatic abscess;" it means the formation of pus between the layers of the broad ligament of the liver.

Frequently, a correct diagnosis can be reached only by repeated and careful study of the case in all its aspects. Golden rules in tropical practice are to think of hepatic abscess in all cases of progressive deterioration of health; and to suspect it in all obscure abdominal cases associated with evening rise of temperature, particularly if there be an upward enlargement of or pain in the liver, leucocytosis, and a history of dysentery—not necessarily recent.

Low-grade pneumonia of the right base in a tropical patient should always be regarded with suspicion, for it may indicate abscess of the subjacent liver.

Perhaps the most common error is to regard the hectic fever of liver abscess as attributable to *malaria*. The regularity with which the daily fevers recur, the daily chilliness, or even rigor, coming on about the same hour, the profuse sweating, and other circumstances so compatible with a diagnosis of malaria, all contribute to this mistake. The periodicity of fever, and a polymorphonuclear leucocytosis should obviate so serious an error.

To mistake other forms of suppuration for liver abscess is not so serious, because in many suppurative diseases the treatment is the same as for liver abscess, and no bad result need follow if diagnosis is not quite accurate.

Intrahepatic suppuration may supervene in *ascaris* infestation, in melioidosis (p. 288), in ascending pylephlebitis secondary to appendix abscess, in diverticulitis and, rarely, in infections with hæmolytic *Staphylococcus aureus*, or very exceptionally with bacillary dysentery. Suppurating abscesses have been reported secondary to duodenal ulceration and enteric infections. Carcinomatosis of the liver, unaccompanied by jaundice, may simulate amœbic abscess. A right perinephritic abscess may have to be considered. In subdiaphragmatic abscess caused by perforation of a gastric or duodenal ulcer, an abdominal swelling can usually be recognized occupying a triangular area on the affected side. Gas is



Fig. 92.—Visualization of amœbic liver abscess by puncture and injection of Ipiodol in erect position. (After Snapper, "Chinese Lessons to Western Medicine.")

usually present and can be recognized by a resonance in the upper part which serves to distinguish it from liver abscess.

Pancreatic cyst elevating the left (less often the right) lobe of the liver may imitate an abscess, but it is not necessarily accompanied by fever. As a rule, it forms a definite tumour of considerable size in the left hypochondrium. Solitary non-parasitic cysts of the liver or polycystic disease may also have to be considered. Phantom tumour may give rise to difficulty, but this gradually disappears under a general anæsthetic.

The presence of *Entamœba histolytica* cysts in the fæces is suggestive but by no means conclusive, of amœbic abscess. They are found in about 45 per cent. of all cases. Occasionally the amœbæ may be cultured from the fæces in cases in which they are not detectable by the microscope.

X-ray examination may confirm the upward enlargement of the liver, and bulging, "tenting" or blurring of the outline of the right dome of the diaphragm and shadowing of the right costophrenic angle indicating effusion. Screening usually shows that it does not move on respiration (Plate XIV). Paradoxical movement (rising with inspiration) is sometimes seen. Should, however, the abscess be situated in the centre of the liver, even if of considerable size, no definite information is usually obtainable by radiography except when the abscess has become partially encysted or calcified (Plate XV), when the outlines become apparent by X-ray. Occasionally, however, the outline of the liver abscess may show up as a less opaque area in the liver substance affording exact location for the exploring syringe. Air may appear in the abscess cavity and show up the fluid level. Injection of air through the aspirating syringe has been practised with success, while lipiodol injection facilitates visualization (Fig. 92). The air-replacement method advocated by Cameron and Lawler (1948) is useful but examination following it should be carried out on the day after tapping. Three radiograms should be taken after screening: in the antero-posterior position, erect; in the lateral position, and in the former position with the patient on the left side. The air outlines the upper part of the abscess and by superimposing the films a correct assessment of the complete size and outline can be obtained. The outline of the diaphragm is blurred when the abscess is near the upper surface of the liver. Normally the upper margin of the hepatic shadow forms a right angle with that of the vertebral column, but when abscess is present this may become more acute.

Liver function tests.—Gutman (1946) found that the serum alkaline phosphatase test is usually positive.

Brem (1955) has investigated this point in 10 cases of amoebic liver abscess in which he used a variety of these tests, including the thymol turbidity and the cephalin, cholesterol and bromsulphthalein tests. All were negative except the alkaline phosphatase and the last-named. In the former 9 units per 100 ml. is the upper limit of the normal, but it was found that values of 8 units were invariably pathological. In 8 cases, the bromsulphthalein tests showed an abnormal retention in 5. This combination is probably due to partial obstruction of the intrahepatic biliary system without extensive cellular damage. The degree of abnormality of these two tests is roughly proportional to the extent of the lesion. Conan (1950) found that this test is normal in amoebic hepatitis, but is increased in liver abscess. Both tests are not invariably complementary so that both should be used in doubtful cases.

Diagnostic aspiration.—To make the diagnosis of liver abscess certain, aspiration must be performed. When the needle enters the liver, an up-and-down pendulum-like movement will be communicated to its outer extremity, in harmony with the rising and falling of the organ in respiration. If the needle does not exhibit this movement, its point may be in an abscess cavity, but such an abscess is not in the liver.

Prognosis.—The prognosis in early operations on single abscess of the liver, provided there is no dysentery or other complication, is good. In multiple abscess, or in single abscess, if there is active dysentery or other serious complication, the prognosis is bad: if there are more than two or three abscesses, it is usually hopeless.

The question of return to the tropics after recovery from liver abscess frequently crops up. If feasible, and if the patient has not to make too great a sacrifice, he ought to remain in a temperate and healthy climate. There are many instances, however, of individuals who have enjoyed permanent good health in the tropics after recovery from liver abscess. Before return the bowel should be thoroughly cleansed of amœbic infection by emetine-bismuth iodide or other treatment. Neglect of this precaution may lead to reinfection and recurrence seven years after the formation of the first abscess.

Treatment.—Hepatitis which has not proceeded to abscess-formation should be treated, especially if dysentery be present or has been antecedent, with full doses of emetine, injected in 1 gr. doses up to a total of 12 gr., and if cysts of *E. histolytica* are present in the stools, by a combined course of E.B.I. and quinoxyl.

Chloroquine diphosphate (aralen) appears to exert remarkable curative properties in hepatic amœbiasis. According to Berliner, it is absorbed from the gastro-intestinal tract and is concentrated in the liver.

Conan has reported upon 22 cases which have been followed up for 24 months. The primary or loading dose of 1 grm. (0.6 of base) is given daily for two days. A maintenance dose of 0.3 grm. is continued for 2-3 weeks. Instances have occurred where this treatment has succeeded where amœbæ were present in the liver pus, in spite of prolonged emetine treatment. Nevertheless the combination of emetine injections and chloroquine by the mouth is well tolerated and is usually successful.

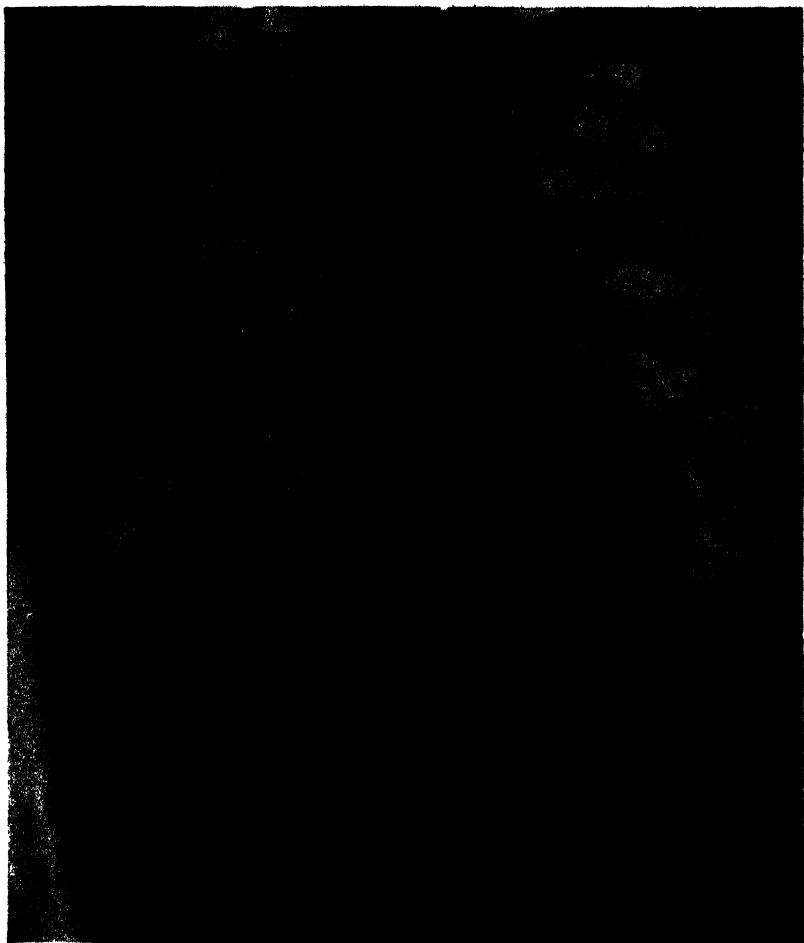
Terramycin (*Oxytetracycline*) is probably the best of the antibiotics in treatment, but though the effects appear to be immediately favourable it is realized that this treatment must be combined with the generally accepted routine with emetine and E.B.I. as stated above. Chenand and Le Henand have recognized this synergic amœbicidal effect and that it affords protection against secondary infections.

When rigor, or hectic fever, or local bulging, or persistent fever and local symptoms give ground for suspecting that abscess has formed, aspiration should be undertaken.

Preliminary aspiration.—When he uses the aspirator the surgeon must be prepared to continue until all the pus is evacuated, or under exceptional circumstances, to operate.

Deep local analgesia usually suffices, but nervous subjects should have gas and oxygen. A medium- or full-sized aspirator needle should be used, as the pus, owing to its viscosity, may not flow through a cannula of small bore.

If there are localizing signs, such as a tender spot, a fixed pain, localized œdema, localized pneumonic crepitus, pleuritic or peritoneal friction, these should be taken as indicating, with some probability, the seat of the abscess and the most promising spot for exploratory puncture. If none of these localizing signs are present, then, considering the fact that the majority of liver abscesses are situated in the upper and back part of the right lobe, the needle should, in the first instance, be inserted in the anterior axillary line in the 8th or 9th interspace but not more than 3½ in. The distance of the inferior vena cava from any part



Radiograph of dome of diaphragm in liver abscess.

(Dr. Carmichael Low.)

LIVER ABSCESS

PLATE XV



Radiograph of certified abscess in right lobe of liver.

— (*Radiograph by Dr. M. Cordiner*)

LIVER ABSCESS

PLATE XVI

of the chest wall is 4 in. The needle swings when the liver is engaged and, as it does so, it should be pushed gently forwards. The operator knows he is in the abscess cavity, because the needle is felt to pass into space. The syringe should then be affixed and aspiration commenced. Effusion of serum into the pleural cavity immediately adjacent to the liver abscess sometimes occurs.

An after course of combined emetine-bismuth-iodide and quinoxyl should be given to eradicate the amebic infection from the bowel.

Open operations.—The indications for open operation are:—

- (1) When after repeated aspiration no pus is obtained, but indications of its presence are too strong to be ignored.
- (2) When an abscess points in the epigastrium, *i.e.*, is situated in the left lobe of the liver.
- (3) When there is a large amount of pus which has been secondarily infected by bacteria and has not yielded to treatment by aspiration.

The route for opening the thoracic or abdominal wall varies according to circumstances as follows:—

Transperitoneal route.—When pus is struck below the costal margin, the aspirator needle is left *in situ* and the abdomen is incised for a length of 3 in. (Kocher's incision), the intestines being guarded with packing. If adhesions are present, a sinus forceps is directed along the needle and pushed through into the abscess, and the blades are opened after withdrawal of the needle. The finger should be inserted into the abscess cavity. When the first gush of pus ceases, the exit is lightly plugged with gauze, the margins of the liver wound are carefully sutured to those of the parietal peritoneum, and the remainder of the wound closed. The gauze plug is now removed, and a wide drainage-tube, provided with a flange and lateral openings, is introduced to the bottom of the abscess cavity. Some surgeons use a wide-bore drainage tube, such as Tudor-Edwards empyema tube drain, pushed right to the bottom of the cavity to prevent extravasation.

Transpleural route.—Should the abscess be struck through an intercostal space, a couple of inches of (the 8th and 9th) ribs had better be resected. The diaphragm should then be stitched to the thoracic wall, or better, to the skin as well, when the abscess may be opened with a forceps. An attempt should be made to stitch the capsule of the liver to the diaphragm. Should the pleura be opened, pneumothorax will result, but this is not necessarily serious. On no account should pus be permitted to enter the pleural cavity.

Sometimes it is simpler to expose the ribs and denude them of tissues. An iodine gauze pack should be inserted underneath the ribs and left for 3 to 4 days. Artificial adhesions are formed in the costophrenic sinus by a process of aseptic inflammation. Shears are then used to resect the ribs. Post-operative drainage is ensured by sinus forceps and a wide-bore tube. Dakin's solution may be used to irrigate as it exerts a solvent action on the liver abscess wall. The modern treatment of introducing penicillin solution into the abscess cavity through a ureteric catheter kept *in situ* has simplified the treatment of secondarily infected abscesses. The initial dose is 25,000 units to 51,000 units in the second week at five-hourly intervals for 15 days (North and Hirschfeld). Hurst recommended the instillation of 50,000 units every 48 hours with remarkable results.

Treatment after operation.—For the first two days after a liver abscess has been opened the discharge is considerable, and the dressing may have to be changed

frequently. Very soon, however, should the case do well, the discharge rapidly diminishes, and the dressing requires renewal only every other day, or every three or four days. During the first week the drainage-tube, provided it be acting efficiently, should not be disturbed, more particularly as it may be difficult to replace. Later, it may be removed and cleaned, and, when discharge has practically ceased, cautiously shortened. *It is a great mistake to begin shortening the tube before it is being pushed out, or so long as there is any appreciable discharge.*

After a liver abscess has been opened and is draining well, temperature rapidly falls, and in a few days, or almost at once, becomes normal. Should fever persist, it is to be inferred either that the drainage is inefficient, or that there are more abscesses in the liver, or that there is some complication. If another

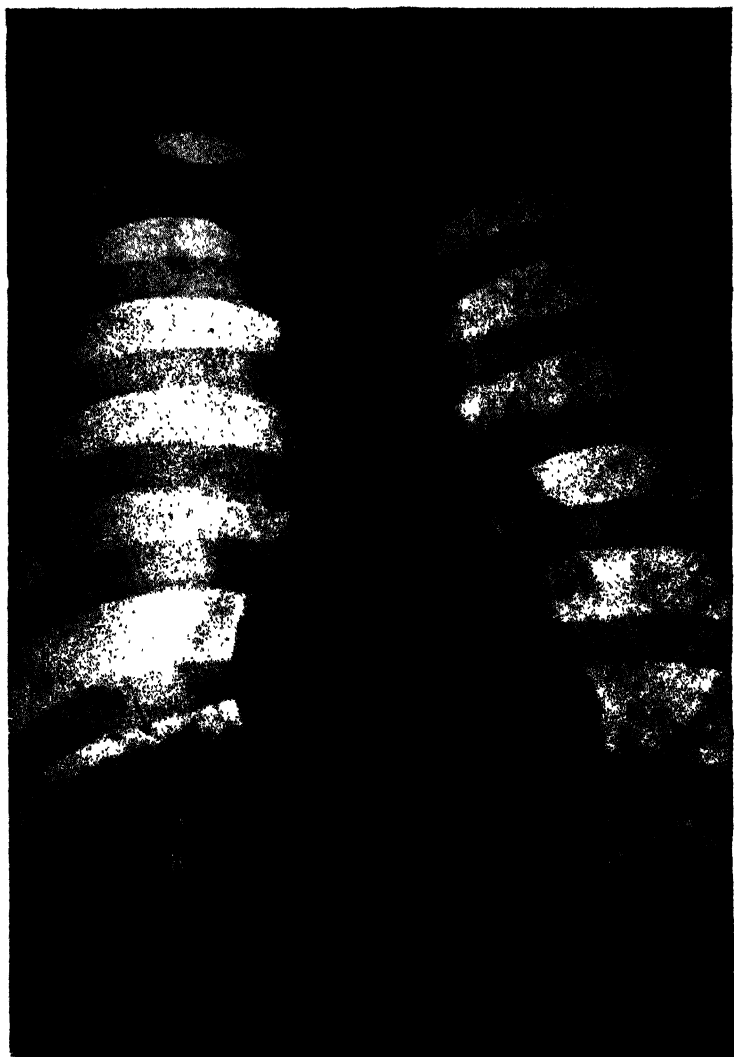


Fig. 93.—Amœbic granuloma and ulceration of abdominal parietes surrounding colostomy.

abscess is suspected, it should be sought with the aspirator and, if found, drained.

It is advisable to give emetine in 1 gr. doses hypodermically, together with chloroquine, both before and after operation, and continue them for a fortnight, whichever operation is employed.

Treatment of abscess discharging through the lung.—If an abscess is discharging through the lung and, although emetine and chloroquine have been freely administered, is not progressing favourably, the question of more efficient drainage by surgical means must be considered. There are two possibilities which render interference desirable: (a) Continued discharge of pus and blood, with or without attendant hectic fever—a condition which, if it persist, will, in all probability, in the end, kill the patient. (b) Not infrequently, prolonged discharge through the lung may induce fibrotic changes, pneumonia, or abscess with all its attendant dangers, such as thrombosis or abscess of the brain. (Plate XVII.)



Radiograph of liver abscess bursting through the diaphragm into base of right lung, whence the pus is being evacuated through a branch of the right bronchus. A—collection of pus in pleural cavity; B—valve-shaped opening through diaphragm at site of abscess in liver. (*Radiograph by Dr. M. Berry.*)

LIVER ABSCESS

Treatment of abscess rupturing into a serous cavity.—When there is evidence that an abscess of the liver has ruptured into the peritoneum, into the pleura, or into the pericardium, the particular serous cavity involved must be opened and at once treated on general surgical principles; otherwise the patient will almost surely die. In the circumstances the surgeon will be justified in assuming great risks.

2. AMOEBIIC ABSCESS OF THE BRAIN, SPLEEN, AND PERICARDIUM

According to Armitage, 48 cases of amoebic abscess of the brain have been recorded, for the most part from Egypt. Like hepatic abscess, it is more common in men than in women. It is generally solitary, and may be regarded as a metastasis of hepatic abscess, though one, unassociated with any other except an intestinal lesion, has been described by Halpert and Ashley (1945). The mechanism by which amoebæ reach the brain is by no means clear. The pressure symptoms resemble those of a cerebral tumour, and the abscess is invariably fatal. Kirk (1956), in Singapore, found at autopsy three large abscesses in the left side of the brain and a smaller one in the cerebellum, the contents of which contained *E. histolytica*. Associated with these was a similar abscess of the liver and extensive intestinal ulceration. Amoebic abscess of the spleen has been recorded by Maxwell, Rogers, Chatterji, and by the Editor. Authentic cases are extremely rare and not necessarily associated with liver abscess. Calcification of the abscess within the splenic pulp may ensue and result in persistent splenomegaly. On the other hand spontaneous splenic abscesses due to infarction or to thrombosis of the splenic artery are, according to Gelfand, quite common in African negroes. Amoebic pericarditis, usually secondary to liver abscess, has been recorded and some 47 cases have been reported in the literature. The Editor has seen one in a child of 2½ in New Zealand. All the cardinal signs of pericarditis were present and a bulging præcordium presented itself from which, on aspiration, pus containing numerous active *E. histolytica* were seen. The father had suffered from amoebic dysentery while on service in the Pacific. There was no evidence of liver involvement, or intestinal symptoms. Norris and Beemer (1956) have described one case with empyema of the left side secondary to liver abscess.

3. AMOEBIIC INFECTION OF THE SKIN, BONE AND SUBCUTANEOUS TISSUES

Since 1892, it has been known that the skin may be subject to amoebic invasion in the vicinity of a discharging liver-abscess sinus. Amoebæ have been demonstrated in sections of the skin, and they are susceptible to emetine. Gangrenous lesions of the abdominal wall and perineum have been described from time to time, especially by Engman and Meleney (1981), while Hu, in China, recorded a series of fourteen cases and showed that the condition is by no means rare. The Editor treated one such case, in which the parietes in the vicinity of a colostomy and the abdominal wall were involved (Fig. 79), with discharge of foetid anchovy sauce pus. The patient was proved to have active amoebic dysentery. Extensive gangrenous destruction of the buttocks and skin of the back was also seen

in St. Mark's Hospital, London, in an ex-soldier who had served in India fifteen years previously; though he had never suffered from clinical dysentery, *E. histolytica* cysts were present in the fæces. The lower part of the rectum, the pelvic floor and the perineal tissues had been destroyed. Response to emetine therapy was quite remarkable (Fig. 94). A recent case from N. Nigeria (1959) was a terrible example. The deep ulceration, with knife-like edge, extended over both buttocks on to the back as high as the wings of the scapulæ. The stench was overpowering,



Fig. 94.—Amebic ulceration of skin. Ulceration of sacrum, coccyx and perineum.

and the tragedy was that it had been mistaken for diabetic gangrene as the victim happened to be a diabetic. This condition was first described by Maxwell as fistulous disease of the buttocks in South China. McConaghey (1945) has published a similar case in a woman with a pararectal abscess spreading to the vagina and perineum.

Amœbiasis cutis is a secondary infection of papillomata around the anus. The lesions have a punched-out appearance, and resemble in this respect intestinal amœbic lesions (Hu).

Morton and Soutar (1947) have found active *E. histolytica* in an abscess

of the buttock secondarily infected with staphylococci in a carrier of *E. histolytica* cysts. There were two ragged cavities communicating with one another. The amœbæ were found lying subcutaneously and there was no connection with the rectum. Norwich and Muskatt (1946) treated an amœbic ulcer of the buttock connected with a pararectal abscess in a negro with amœbic dysentery. Rose (1952) found an abscess in the middle third of the femur extending down to the bone. *E. histolytica* was found in the pus and the lesion was cured by emetine.

4. GENITO-URINARY AMŒBIASIS

A number of uncritical papers have appeared describing as amœbæ large prostatic or other inflammatory cells which may be present in subacute cystitis or prostatitis, but occasionally vegetative forms of *E. histolytica* are found in the urinary sediment, sometimes derived from a fistulous track between the ulcerated rectum and the bladder (Craig). Amœbic ulceration of the urethra in the male, as well as of the cervix uteri in the female, have been reported by Hu in China, and amœbæ have been demonstrated in the tissues in microscopic sections; *E. histolytica* in the urine may be derived from this source, but an amœbic abscess of the epididymis has been reported from China by Warthin. Murgatroyd treated one extraordinary case where amœbæ were present in all specimens of urine passed, although no lesions of the bladder could be visualized by cystoscopy. The organisms were apparently derived from the vesiculæ seminales. This is all the more exceptional as Watson and others have shown that *E. histolytica* cannot survive in urine. Rose (1946) originally described amœbic vaginitis in China. There were inflammatory œdema of the vaginal wall with ragged ulcers.

Amœbic ulceration of the vagina is not uncommon in India. Misra described two in 1950 and two more in 1953. Danaraj, in Singapore, has collected some fifteen recorded instances from India, Hainan, Borneo and Mexico. Sometimes the cervix uteri is involved and amœbic infection may be superimposed upon previous carcinomatous ulceration. The cervix is covered with offensive sloughs and superficial snail-track ulcers with undermined edges can be demonstrated. All are unanimous in the rapid and specific action of emetine in these conditions.

5. PULMONARY AMŒBIASIS

This type of case is distinct from pulmonary abscess secondary to that of the liver where infection of the lung tissue results from direct extension of the hepatic abscess, or by rupture, into the bronchus.

In primary pulmonary amœbiasis the amœbæ reach the lung by direct embolism from the bowel. Having gained the pulmonary circulation, they form firm nodules, which later break down into small abscesses. The symptoms produced closely resemble those of a fugitive broncho-pneumonia, or some form of tuberculous infiltration.

These patients, who have been at some time the subjects of amœbic infection, suffer from pulmonary symptoms, with profuse purulent expectoration, sometimes tinged with blood, and respiratory distress with intermittent pyrexia. They are prone, however, to rigors, which may serve to differentiate the condition from other respiratory diseases. The physical signs vary, but are usually those of broncho-pneumonic consolidation, detectable at the border of the scapula, especially on the right side. Skiagraphy may be of little avail in diagnosis. Amœbæ

Siberia, China (Tsingtau), Georgia, the Philippines, Cochin China, Andaman Islands, Hawaii, Mauritius and Rodriguez, Belgian Congo, Egypt, and the Sudan. Cases have also been reported from North America, North and South Carolina, England and Ireland. McCarey (1952) reported a series of 87 cases from Abadan, S. Persia. There was no connection with pigs.

Pathology.—There is little or nothing to distinguish the gross as well as the microscopic pathology from that of amoebic ulceration. The organisms have been found by Strong, Martini and Walker in the mesenteric glands. In thirty autopsies a variety of dysenteric lesions, from catarrhal congestion and diphtheritic patches to extensive ulceration, have been described. On section, Strong demonstrated the balantidium, not only in exudates on the surface of the bowel, but congregated in large numbers in the follicles, or embedded in the tissues forming the base of the ulcerations, including the submucosa, muscular coats, and even in the lumen of blood-vessels and lymphatics. The early lesions are minute hæmorrhages; later, ulceration and abscesses appear. Bowman stated that the colon throughout its whole extent may be a mass of ulcers from which hang shreds of necrotic tissue—lesions resembling those of amoebic dysentery.

Symptoms.—These are, in the present state of knowledge, indistinguishable from those of amoebic dysentery. The disease is chronic, its special nature being discoverable only on microscopic examination of the stools. Generally, only one or two balantidia are found, but as many as twenty may be seen in every field of the microscope. The blood usually shows no change; there is no leucocytosis and the polymorphonuclears represent 70 per cent. The ulcerations in the bowel, revealed by sigmoidoscopy, resemble those of intestinal amoebiasis as described by Mazza, Alvarado and Schürmann (1932). The mortality in 111 cases collected by Strong was 29 per cent.

Treatment.—Young and Burrow (1943) claimed to have cured seven cases with carbarsone, 0.25 grm. twice daily for 10 days. This should be repeated if there is relapse. Methylene blue enemata, 2 pints of a 1 per cent. solution, are claimed to give good results. Westphal praises *Acranil*—hydrochlorate of acridine (see p. 866). Shun-Shin (1947) claimed cures from intramuscular injections of $\frac{1}{4}$ gr. of biniodide of mercury and this has been confirmed by Pramanik. *In vitro* a 1 : 100,000 solution killed the balantidia instantaneously and retention enemata in this strength were well tolerated. For children the dose by intramuscular route is $\frac{1}{4}$ gr.— $\frac{1}{10}$ gr. and for the adult $\frac{1}{4}$ gr. McCarey recommends acetarsol, 4 gr. three times daily for 5 days, and Brummer tablets of 2-phthalylsulphanil-aminothiazole; Weinstein and others gave *terramycin* in divided doses over 10 days. The total is 17 grm.

III. HELMINTHIC DYSENTERIES

Schistosomal dysentery.—Adeno-papillomata or ulcerations of the large intestine evoked by passage of eggs through the intestinal wall, are found in *Schistosoma mansoni*, *S. japonicum*, and exceptionally in *S. hæmatobium* infestations. The dysentery thus produced is met in those countries in which the parasites occur.

Infection with *Cæsothogostomum apiostrum* and *O. stephanostomum* (pp. 986, 987).—These are rare intestinal parasites of man in Brazil, Northern Nigeria, Central Africa and Indonesia. When numerous they may give rise to dysenteric symptoms. The adult worms encyst under the submucosa, and may, together with their eggs, be recognized in the dysenteric discharges. Nodules in the cæcum and ascending colon have been described by Lie Kian Joe.

Infection with other helminthic parasites.—Chronic diarrhoea and possibly dysenteric attacks have occasionally been noted in intestinal infections with *Fasciolopsis buski* (p. 942), *Paragonimus ringeri* (p. 948), *Heterophyes heterophyes* (p. 947), and *Strongyloides stercoralis* (p. 990).

DIFFERENTIAL DIAGNOSIS OF THE DYSENTERIES

Mixed infections of different forms of dysentery may, of course, occur in those countries in which these diseases are endemic.

Combined infections of amœbic and bacillary dysentery are the most frequent. Such cases do not usually occur in temperate countries, but during the course of severe epidemics of bacillary dysentery, when bacillary infection may be grafted upon some long-standing amœbic ulceration of the bowel. On the other hand, this dysentery may be followed by amœbic invasion of the bowel, which renders diagnosis still more difficult.

Bacillary dysentery occurs quite commonly as a terminal event in intestinal schistosomiasis, and amœbic ulcers may sometimes be associated with the same condition.

Giardiasis.¹—Of the intestinal flagellates which appear in the fæces, perhaps *Giardia (Lambia) intestinalis* has the best claim to be regarded as pathogenic. The usual habitat of the parasite is in the upper part of the small intestine, but it may also heavily infest the duodenum. When recently passed in the fæces it is very active, presenting a characteristic appearance. During the passive stages cysts appear in the fæces in enormous numbers, and sometimes may be found associated with those of *E. histolytica*. *Giardia* cysts are generally found in 4–16 per cent. of normal natives of the tropics. Other species are found in mammals and in reptiles, and one in the mouse, *Giardia muris*, is closely allied to the human parasite. In children in Northern countries giardia infection is three times as common as in adults. (In America 48·1 per cent. of industrial school children.) For a description of *G. intestinalis*, see p. 539.

In England and in Canada the parasite has been found in the intestine of quite a large number of normal children, while Boyd, Silverman, and others have shown that it can occasionally be demonstrated in the duodenal juice, bile, and gastric contents.

Some regard this parasite as pathogenic on the grounds that it is found in large numbers when the stools are liquid, and that quantities of mucus are passed containing active parasites.

Giardia infection is associated at times with a type of recurring diarrhoea accompanied by abdominal discomfort. The stools may be of a peculiar clay colour and pultaceous consistence, and may resemble those of tropical sprue, or in English children, those of coeliac disease (R. Miller, 1926). Fat absorption has been found defective and excretion of bile below normal; both are attributed to mechanical effects of these parasites on the intestine. After these attacks, the encysted forms of *G. intestinalis* are present in large numbers in the fæces. Relapses tend to occur periodically, but eventually tolerance is acquired. Flatulence is almost invariable. In the acute stage the abdomen is tender and there is general discomfort. Véghelyi, who made observations on children in Budapest, described anorexia, headaches, dizziness, abdominal pains, anæmia, and steatorrhœa. The attack is not accompanied by emaciation, and symptoms probably originate from mechanical irritation, not from destruction of the mucosa, though

¹ Giardiasis or lambliasis is mentioned in this section for the sake of completeness, although the diarrhoea associated with the parasite cannot strictly be classified as a dysentery.

in mice, in which similar parasites cause diarrhoea, they may penetrate the sub-mucosa. *Giardia* infections are intractable and may persist for years. Hegner thought that the number of these parasites is dependent upon the diet as they tend to disappear from the faeces when the patient is fed on a protein dietary. Chenau (1955) found trophozoites of *G. intestinalis* in 18 out of 293 persons in bile obtained by duodenal intubation. It is therefore apparently true that the parasite may invade the biliary tract, but there is no positive evidence that it causes cholecystitis.

Treatment.—It is difficult to be certain of complete extirpation of these protozoa, for giardia frequently reappear in numbers in the faeces after an absence of several months. Apparently the parasite itself is subject to periods of great activity followed by periods of quiescence.

Atebrin (*mepacrine*, *quinacrine*) is specific, both for the active phases of the parasite and for the cysts. This claim, originally put forward by L. Brumpt, has been abundantly confirmed from many sources. The parasites disappear from the faeces after a course of 0.1 grm. three times daily for 5–7 days, in adults; though in children two tablets daily suffice. Sometimes it may prove necessary to repeat the course. Probably giardia is mildly pathogenic, because associated symptoms also disappear after treatment. German and Scandinavian authorities prefer *Acranil*, the hydrochlorate of an acridine compound, in doses varying from 0.25 grm. daily for children under two, to 1.5 grm. daily for 5 days in those over ten. This drug is said to be more easily tolerated than atebtrin.

Nivaquine, 0.3 grm. daily was recommended by Carri and Shisani in 1950; but other 4-aminoquinolines are now replacing atebtrin in treatment. Camoquine (*amodiaquin*), 0.6 grm. in a single dose for adults and 0.2 grm. for children for 2 days, and chloroquine in doses of 0.3 grm. for adults for 5 days and children 0.2 grm. for the same period are recommended by Konan, Lamadrid, Montemayor and others (1954). Bacigalupo (1956) in the Argentine states that amodiaquine should be used only in cases of intolerance to the acridine salts.

OTHER FORMS OF DIARRHOEA AND DYSENTERY ASSOCIATED WITH INTESTINAL PARASITES

The common intestinal flagellates, *Trichomonas intestinalis* and *Chilomastix mesnili* (see p. 937), though occurring commonly in diarrhoeic and dysenteric stools, have little claim to pathogenicity. They are frequently present in large numbers in the fluid faeces of patients convalescing from bacillary or amoebic dysenteries. Probably the presence of large numbers of these flagellates in the bowel contents is due, to a great extent, to the fluid medium in which they flourish; but when a case of chronic diarrhoea is encountered and no other obvious signs can be found, and where large numbers of active flagellates are lashing about in liquid faeces, it becomes difficult not to assign some pathogenic properties to these apparent agents of disease. Hence the term **Flagellate Dysentery** has arisen—a term which probably indicates that the host has been exposed to abnormal intestinal infection. These organisms usually disappear after vigorous lavage of the bowel by irrigations of 2 per cent. sodium bicarbonate combined with stovarsol (gr. 4) (spirocid) in similar dose—two tablets daily for eight to ten days.

Spirochætal dysentery is attributed to the presence of numbers of spirochætes in the intestinal canal. These organisms, composed of three or more simple

spirals, are known as *Spirochæta eurygyrata*, but they are not usually regarded as pathogenic.

Intestinal coccidiosis has to be considered, especially *Isospora hominis* (see p. 904), which causes diarrhoea, with mucus and Charcot-Leyden crystals in the fæces and usually eosinophilia. Cases of this infection have been reported from all over the world, especially from the Near East and Indonesia.

Malarial *dysentery.—A blood-stained discharge or, more frequently, hæmorrhage, may occur in the abdominal forms of subtertian malaria. The blood passed is very dark, due to petechial hæmorrhages from the intestinal mucosa. These are, as a rule, very serious cases. Instances were recorded by the Editor, in which malaria was first suspected from discovery of the subtertian parasite within the red blood-corpuscles present in the fæces.

Kala-azar dysentery.—Blood and mucus may be passed in the fæces in advanced cases of this disease, which may be due to an ulceration of the bowel by Leishman-Donovan bodies.

Other conditions which may resemble dysentery.—There are other perhaps more familiar conditions, not necessarily of tropical origin, in which dysenteric symptoms may occur

Of all common diseases with which mild dysentery may be confused, the first place must be given to *internal hæmorrhoids*. A correct diagnosis is readily made. Again, profuse offensive diarrhœic motions with blood and mucus may be passed in *tuberculous ulceration* of the large bowel, which may be comparatively common in the tropics. *Colitis*, ulcerative, membranous, or *hæmorrhagic*, resembles bacillary and amœbic dysenteries in clinical features and in the character of the stools, but can be differentiated by microscopic examination of the fæces, as well as by sigmoidoscopy. Idiopathic ulcerative colitis (colitis gravis) is becoming increasingly common and has to be differentiated from the bacillary dysenteries. It is undoubtedly a disease *sui generis* and is distinguished by pyrexia, toxæmia, intense anæmia, a tendency to spontaneous remission, and great liability to relapse. A very acute form sometimes follows cystoscopy, or instrumental investigation of the genito-urinary tract, and has been shown to be due to mercury poisoning from instruments sterilized with mercuric cyanide. *Mucous colitis*, or the syndrome which is commonly known by that name, is a frequent sequel of both bacillary and amœbic dysentery and is frequently confused with both. Stercoral ulceration, produced by chronic constipation associated with myxœdema, may give rise to a blood and mucous discharge. Certain surgical conditions—simple polypus, malignant disease, intussusception, even syphilitic disease of the rectum, or rectal stricture in lymphogranuloma inguinale (p. 629)—the diagnosis of which should be determined by digital examination—must be kept in mind. *Polyposis* is a very distressing condition which usually undergoes malignant degeneration. Foreign body in the rectum is another possible diagnosis.

Blood and mucus are often passed in *diverticulitis*.—In *paratyphoid B.* infections ulceration of the large intestine may give rise to blood and mucus in the stools. *Food poisoning* due to organisms of the *Salmonella* group may sometimes cause confusion by producing somewhat similar symptoms.

CHAPTER XXXIII

TROPICAL SPRUE AND HILL DIARRHŒA

Synonyms.—Tropical Diarrhœa ; Aphthæ Tropicæ ; Psilosis ; Ceylon Sore Mouth.

Definition.—A peculiar and dangerous form of chronic disturbance of function of the whole or part of the mucous membrane of the small intestine. Although essentially a disease of warm climates, tropical sprue may develop for the first time in temperate countries in individuals who have previously resided in the tropics or subtropics.

Geographical Distribution.—(Map IX)—South China, Philippines, Cochin China, Japan, Java, the Straits Settlements, Ceylon, India, Mauritius, a few cases from Fiji, more frequently in the West Indies, the Southern United States, Puerto Rico, Central America, the Guianas, and Queensland. Isolated cases have been recorded from Iraq, Egypt, Palestine, North Africa and Russian Turkestan. In Central, West and East Africa it is problematical whether tropical sprue does occur, though Gelfand claims to have seen a sprue-like disease in Europeans in Rhodesia. During the 1939–1945 war cases in British soldiers have been seen from the Mediterranean—Malta, Southern Italy and Gibraltar.

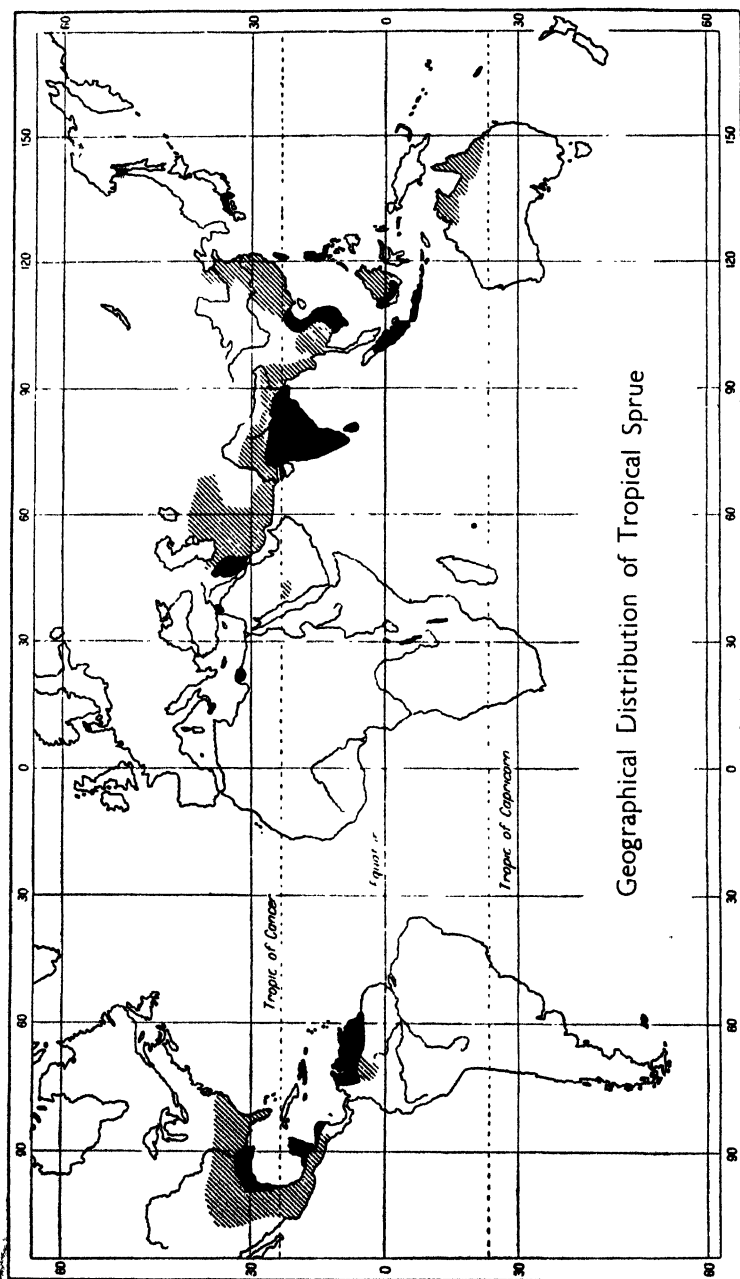
Epidemiology and endemiology—Information so far on this subject suggests that tropical sprue is a regional, as opposed to a climatic, disease and it pre-eminently affects Europeans. There was formerly some doubt of its existence in native races. Highly pigmented races, usually the indigenous inhabitants of the endemic country, are usually less liable than immigrants, though tropical sprue was prevalent in Indian troops in Burma in 1944–45.

The disease is apt to occur in one or more members of the same family. Many instances of sprue in husband and wife have been recorded, probably from exposure to the same influences. During the Burma campaign, 1943–45, sprue occurred in epidemic form in British troops (*see below*). Atmospheric temperature *per se* has no influence, for sprue originates at high altitudes in Ceylon and in the Himalayas, where the climate approximates to that of Europe.

There are residences in Bombay and bungalows in Ceylon which were notorious for the incidence of sprue in successive tenants; these have been known as “sprue houses” and have given rise to a popular theory that the disease might have been connected in some way with “dry-rot” in wooden beams.

Tropical sprue attacks those of middle age or over. Children are rarely affected, though there is one authentic record in an English boy from Ceylon of eleven years of age (Miller). Amongst Europeans both sexes appear equally liable.

Ætiology.—A nutritional deficiency, as originally postulated by McCarrison, Elders and Nicholls, at one time appeared to be the most



likely factor. Discoveries on the ætiology of pellagra and the fact that in fully developed tropical sprue there are signs and symptoms which may be ascribed to vitamin deficiency, mainly of the vitamin B₂ complex, tended to fortify this theory, but these are most probably secondary manifestations. Tropical sprue is undoubtedly a disease *sui generis* with clinical characteristics so typical as to admit no other assumption. The arguments for a virus infection have been stated by the Editor in the *Lancet* (1953), 2, 889.

Biochemical studies suggested that the phenomena of tropical sprue can best be explained in terms of a metabolic breakdown of the gastro-intestinal tract, characterized by defective absorption in the small intestine primarily connected with defective secretion of Castle's intrinsic factor. The well accepted fact that the anæmia of sprue resembles that of pernicious anæmia, and responds in like manner to the extrinsic factor (in liver extracts), is regarded as suggestive.

It was postulated by Bennett that the sprue syndrome may be a "*chronic jejuno-ileal insufficiency*" of which the outstanding signs are steatorrhœa, emaciation, meteorism, glossitis and megalocytic anæmia; and that these phenomena may be evoked by a number of conditions. The main argument for this view lies in the results of gastro-jejuno-colic fistula, which reproduce the main signs and symptoms of sprue, whilst these sprue-like signs and symptoms disappear when the defect is remedied by operation. Sprue symptoms may also supervene on resection of four feet, or more, of the lower ileum (Markoff), or may be produced by interference with chyle absorption in lymphadenomatous infiltration of the mesenteric glands, or by gross ulceration of the ileum: facts which suggest that some of the clinical features of sprue are attributal to defective absorption from that viscus. This is backed up by the pathology and the withering of the intestinal villi.

Other diseases closely simulate tropical sprue, such as cœliac disease in children and idiopathic steatorrhœa in adults. These are probably the outcome of other forms of malabsorption from the small intestine, whilst the latter has been shown by Frazer to be caused in some manner by the gluten of wheat. It is conceivable that the full syndrome is produced, not so much by the absence of essential vitamins from the dietary, as by failure to absorb them, or by lack of biosynthesis in the bowel owing to abnormal bacterial flora. The selective nature of the vitamin-B deficiencies—nicotinic acid, riboflavin, pyridoxin and folic acid—is striking. All these are essential growth factors for bacteria, especially those known to be present in the small intestine in sprue. These bacteria absorb the available vitamins causing deprivation of these factors in the host.

Obscure as the true ætiology of tropical sprue appeared to be before 1939 it must be confessed that the outcome of the most diverse and detailed investigations which have been carried out by special teams of observers from 1942-45 in India and Burma have rendered the problem even more difficult of clarification. There, as is abundantly clear from the writings of Leishman, Keele and Bound, Black and Fourman and many others, tropical sprue in British troops behaved as an epidemic disease with an incubation period and a seasonal incidence. There were many opportunities for observation because sprue appeared on an unprecedented scale in many widely separated areas, quite unconnected with dietetic or climatic factors. It had a distinct regional distribution. For instance, though so prevalent in India and Burma, it was practically absent from the far greater numbers of combatants, American, British and Australian in the Pacific combat zones. These cogent facts appear to offer no other argument than that in its initial stages tropical sprue may behave as an infectious disease due to some

undiscovered virus and that only in its later stages do the signs and symptoms of an avitaminosis become apparent. Leishman relates that in 1944 some 675 British troops had to be invalided to England on account of severe sprue. Whilst amongst Indian troops a similar malady appeared on a big scale and was termed (quite unnecessarily) "para-sprue" (Napier, Chaudhuri, Ayrey). Contrary to previous experience the length of stay in the tropics proved scarcely a factor. Three-quarters of the cases had less than two years' service. Some developed sprue within two weeks of arrival and one was taken off a transport on arrival in India with the fully developed sprue syndrome.

In East India the sprue season lasted from March to September with a peak incidence in June, but in areas of lesser incidence the season was less restricted. These months corresponded to the fly season and coincided with an outbreak of bacillary dysentery, but it was not a sequel to this disease. For instance, a previous dysenteric infection was obtained only in 9 per cent. In 1943 in Chittagong 50 per cent. of one unit developed the disease within three weeks of arrival. As regards the geographical distribution 65 per cent. of cases originated in Bengal, Assam and Burma; 15 per cent. came from West India; 13 per cent. from South India and Ceylon, and 5 per cent. from North India. At least one-third were in soldiers living under good conditions on full rations and often in an innocuous climate. In more than half the cases the full sprue syndrome was established within two months of onset of diarrhœa.

Fat is mainly ingested as triglyceride in emulsion in the lumen of the small intestine. The emulsifying system is dependent on a triple combination—fatty acid-bile salt-monoglyceride. The intestinal contents of all varieties of fat-absorption have shown normal dispersion of fat and normal enzyme activity. Frazer and his colleagues have shown that, though malabsorption of fat is the most conspicuous feature in tropical sprue, yet other elements of the diet are equally implicated.

It is becoming abundantly clear that, though other steatorrhœas bear some resemblance to tropical sprue, their basic aetiology may be quite dissimilar. What then is the outcome of all these investigations?

There are certain features of tropical sprue which are very distinctive and for which some specific factor must be postulated. There are the typical tongue and mouth lesions and the aphthæ which suggest the presence of some infective virus. The geographical distribution is quite peculiar and a disease with such a limited range suggests a specific and distinctive cause. The primary manifestations of tropical sprue suggest also some infective agent, such as a virus, which acts upon the alimentary tract and interferes with absorption and which in turn leads to secondary manifestations due, apparently, to vitamin deficiencies. This suggestion is supported by the work of the U.S. Army's sprue team in Puerto Rico (1959).

The *latency* of tropical sprue is a feature which is difficult to explain on any dietetic or nutritional basis. It is well known that the disease may appear *de novo* in persons who have at one time resided in an endemic area 14 years or longer after their return to a temperate climate. Furthermore remissions of the disease may ensue and sprue symptoms recur, sometimes of short duration after an interval of 10 years or longer.

Other suggestive facts centre round the disappearance of the disease from many of its old haunts during the last twenty years. In Singapore it is said to have almost disappeared since the introduction of deep refrigeration. In Ceylon, too, tropical sprue, which was the scourge of the tea plantations, hardly any longer occurs. Finally the true import of the recent work of French, Gaddie and Smith (1956) on the effects of combined antibiotic therapy on the course of the disease still remains to be assessed (see p. 520).

PATHOLOGY.—The heart has usually undergone "brown atrophy." The liver is atrophied, sometimes with fatty changes, and all the muscles and viscera are anæmic and wasted. With these exceptions and certain changes in the alimentary tract, so far as is known, there are no special lesions invariably associated with this disease. Occasionally, the pancreas shows fatty or granular degeneration of the cells, with softening of isolated acini and slight inflammatory infiltration of the connective tissue. These, however, are not more constant than are similar changes occasionally found in the liver and kidneys. Sections of the tongue show desquamation of the epithelium, especially from the surface of the fungiform papillæ.



Fig. 95.—Section of the ileum in tropical sprue, showing shrinking, deformity of the villi and round-cell infiltration of the mucosa. (*P.H.M.B. orig. Ceylon, 1915.*)

Lesions of the alimentary tract.—In longstanding cases there is usually patchy atrophy of the small bowel so as to render it almost diaphanous. Ulceration and erosion of the ileum leading to perforation and peritonitis have been described by the Editor, but are probably secondary changes.

The chief lesions are seen in the villi of the jejunum and ileum. They are so characteristic as to explain the clinical and pathological features of tropical sprue. K. Justi (1918) in an autopsy in Hong Kong, where precautions were taken about postmortem decomposition, described shortening of the villi which he thought was due to autolysis. The Editor

in Ceylon (1915), taking similar precautions by removing specimens of the small intestine immediately after death, described flattening and deformation of the villi which had become shrunken and irregular in shape. The epithelium was intact, but vacuolated, with well-defined brush border (Fig. 95). Goblet cells were numerous and the fundi of Lieberkühn's follicles distended. The interstitial tissues were infiltrated with round and plasma cells. It remained for Paulley in 1954 to confirm these findings by biopsies performed at laparotomy. M. Shiner (1956), by improving the apparatus for gastric biopsy, guided fluoroscopically, obtained specimens from the jejunum in two cases of tropical sprue. The changes in the villi resembled in every detail those described by the Editor in 1915. Since then biopsies of the jejunum have been performed on a considerable scale by the U.S. Army's sprue team in Puerto Rico and the changes in the villi are described by F. H. Gardner and C. E. Butterworth which agree entirely with that described above. The intestinal biopsy capsule employed was devised by Lt.-Col. W. H. Crosby. More recently M. Shiner (1959) has been able to observe the regeneration of the villi after administration of folic acid. The importance of the villi in the absorption of fats and proteins is well known. Recently Baker (1958) has shown that an important function is the absorption of vitamin B₁₂. The villi are elevations of 1 mm. by 0.1-0.25 mm. and number 10 to each sq. mm. of the mucosal surface. They are finger-like and in a state of continuous movement, stimulated by a hormone-villikinin. The contractions occur 3-6 times a minute. It is probable that in sprue the normal physiology of the villi is interfered with and this explains the steatorrhoea, the anæmia and the wasting.

As originally shown by the Editor in Ceylon secondary infection of the intestinal tract with the thrush fungus, *Candida albicans*, is not an infrequent terminal event. There is an over secretion of mucus throughout the intestinal tract, more especially in the small intestine where this fungus grows.

Clinical pathology.—The stools of sprue are characterized by their light colour and excessive size; they may be five or six times the normal amount. Analysis reveals the ordinary elements of bile, notwithstanding the lack of colour. The excess of fat in the stools and low fat content of the blood (41.28 mgm. per cent.) indicate that a proportion is due to actual excretion of fat through the intestinal mucosa. (The normal is 600 mgm. per cent.). Normally, neutral fats in the fæces are to fatty acids in the proportion of 1 to 2; in pancreatic disease this ratio is reversed, and may be as high as 15 to 1; while in sprue stools more splitting of fats takes place, the proportion of neutral fats to fatty acids being as 1 to 3 or even 1 to 5. It is estimated that not uncommonly 50 grm. of fat is excreted in a single stool when the patient is existing on a mixed dietary. The average results of fat analysis of fæces is as follows:—

Total fat	60 per cent.
Combined fatty acids	14	" "	
Free fatty acids	...	87	" "
Unsoaped fat	...	45	" "
Neutral fat	...	7	" "

High faecal fat above 50 per cent. does not denote clinical severity (Keele and Bound). Many observers have insisted that in early cases there is no actual steatorrhœa. Samples of stools taken at different intervals vary very much in their fat content. It is necessary to collect all the specimens passed in twenty-four hours. Others insist that an average analysis should be made from stools collected over a period of five days. The fat intake for a period of at least three days should be known. Pallor of faeces may be due to alteration of the colour of the bile pigment (leucourobilin) and not necessarily due to fat.

Howell (1947) finds that in early cases, whilst the total faecal fat is often within normal limits there is a significant rise in the split : unsplit fat ratio.

The blood picture of the fully-developed tropical sprue case is a megaloblastic anæmia, the size of the cells varying from 7·8–8 μ . The very variable degrees of anæmia coincide with the megaloblastic arrest in the bone marrow, as seen by sternal puncture, but this is definitely less than that found in pernicious anæmia. In severe cases the marrow picture may be definitely hypoplastic. As a general rule, this grave anæmia occurs in patients over fifty years of age. In no instance, in the cases investigated, has the colour index been less than 0·7, but in the majority it is above that figure. In uncomplicated sprue the leucocyte counts are either normal, or there is a leucopenia associated with a relative lymphocytosis. Blood crises commonly occur and are characterized by a rapid and critical fall in the hæmoglobin and red blood-corpuscles. Usually, associated with severe diarrhœa, it progresses to a fatal issue, without remissions and without those evidences of blood regeneration which are so typical of similar crises in pernicious anæmia. Hyperbilirubinæmia is found more frequently in malaria and in pernicious anæmia than in tropical sprue (Van den Bergh test).

The Price-Jones curve resembles that of pernicious anæmia, being characterized by marked asymmetry, broadening of the base, displacement to the right, and a definite increase of the diameter of the corpuscles to 8·07 μ . It therefore seems that deficient blood-production rather than excessive blood-loss constitutes the basis of sprue anæmia.

Blood-sugar regulation.—Thaysen originally pointed out that in sprue, as well as in idiopathic steatorrhœa and cœliac disease, there is an abnormally low blood-sugar curve, which is not due to impairment of glucose absorption, or to its destruction in the intestines. On the other hand Maegraith and colleagues (1946) have shown that the fructose curve under similar conditions is normal. Fructose is absorbed by simple diffusion.

The urine is highly coloured, especially in cases with pronounced anæmia. This is due to the appearance of urobilinogen and urobilin in pathological amounts, derived from the products of blood destruction, as it is estimated that in sprue anæmia the blood-cells are being destroyed nearly five times more rapidly than normal. The diastatic reaction has been investigated and has been found to be well within the normal limits. This method affords a means by which sprue may be differentiated from chronic pancreatitis. In acute sprue there is porphyria, as in pellagra.

Gastric secretion.—In most cases there is a relative hypochlorhydria or a normal acid curve, but occasionally hyperchlorhydria may be present. In cases with severe anæmia there is usually *achylia gastrica*, but the gastric elements

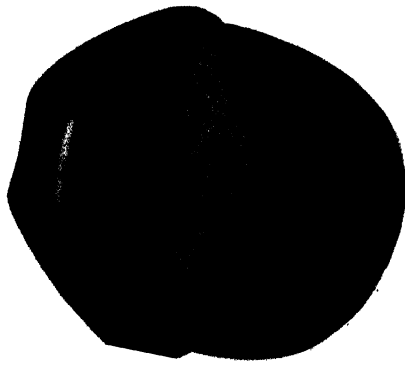
differ from those of pernicious anæmia in that acidity in sprue returns to normal after adequate treatment with liver extract and restoration to health.

Salt deficiency occurs in patients with low blood pressure, asthenia and signs of peripheral circulatory failure. These have low serum sodium and serum chloride levels. The plasma volume is low in relation to body weight. There is an abnormal loss of sodium, and to a less extent of chloride when the patient is put on a high intake of salt. Sodium and chloride are both retained and the serum chlorides rise to normal. The blood pressure rises and clinical signs of dehydration disappear, whilst fat loss in stools is unaffected. The loss of electrolytes in the copious watery stools is the main cause of salt deficiency (Black).

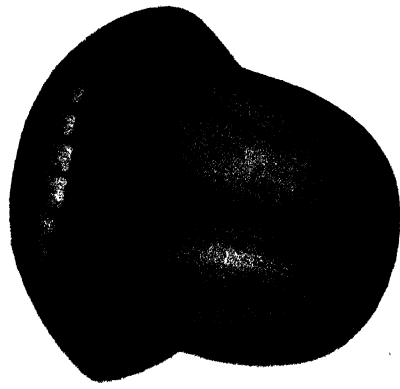
Symptoms. *General symptoms in a typical case.*—In an ordinary fully developed case the patient—who is generally dark or muddy in complexion and much emaciated—complains of three principal symptoms: soreness of the mouth, dyspeptic distension of the abdomen, and looseness of the bowels—the last being particularly urgent during the early morning and part of the forenoon. He may also complain of feeling physically weak, of loss of memory, and of inability to take exercise or to apply his mind. His friends will probably volunteer the information that he is irritable and unreasonable. In addition to patchy pigmentation and general discolouration of the skin, dryness with depilation is common, as is also scaling of the parakeratotic type. This follicular hyperkeratosis responds quickly to treatment.

Mouth lesions.—The soreness depends on a variety of lesions of the mucous membrane, which, though painful, seem to be very superficial and vary considerably in intensity from day to day. During an exacerbation the tongue looks red and angry; superficial erosions, patches of congestion, and perhaps minute vesicles appear on its surface, particularly about the edges and tip. Sometimes, from the folding consequent on swelling of the mucous membrane, its sides have the appearance of being fissured. The filiform papillæ cannot be made out, although here and there the fungiform stand out, pink and swollen (Plate XVIII). If the patient be made to turn up the tip of the tongue, red patches of superficial erosion, sometimes covered with an aphthous-looking pellicle, may very likely be seen on either side of the frænum. These aphthæ probably form beneath the epithelium and subsequently burst. On eversion of the lips, similar patches and erosions are visible; and, if the cheek be separated from the teeth, they may be seen on the buccal mucous membrane. Occasionally the palate is similarly affected; very often, also, the mucous follicles are enlarged, shotty, and prominent. The gullet and uvula may also be congested and, in places, raw and sore. "Cheilosis," or tissue paper-like changes on the lips, and angular stomatitis are seen in about 20 per cent. of cases in acute sprue.

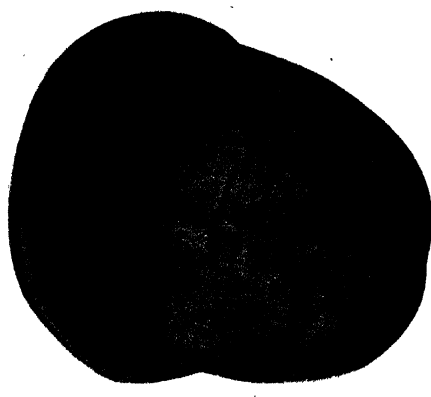
In consequence of the irritation caused by these superficial and exceedingly sensitive lesions, the mouth tends to fill with a watery saliva, which may dribble from the corners. If the patient attempts to take any acrid food, strong wine, or anything except the very blandest diet, the pain and burning in the mouth are intolerable; so much so that, although perhaps ravenously hungry, he shirks eating. Not infrequently, swallowing is accompanied and followed by a feeling of soreness and burning under the



Avitandocis (B2) tongue (prepellagrous),
showing angular stomatitis.
PLATE XVIII



Acute stage of sprue with typical aphthae.
(P. Manson-Bair)



Chronic sprue tongue

PREPELLAGROUS AND SPRUE TONGUES

sternum, suggesting that the gullet, like the tongue, is also irritated, raw and tender. During exacerbations the condition of the mouth becomes greatly aggravated. Although during the temporary and occasional improvements it is much less painful, even then salt, spices, strong wines and all kinds of sapid foods sting unpleasantly ; and the tongue, particularly along its centre, is seen to be bare and polished as if brushed over with a coating of varnish. At all times the tongue is abnormally clean and devoid of fur ; during the exacerbations it is red and swollen ; but during the remissions, and when not inflamed, it is small and pointed, and, owing to the anæmic condition of the patient, it may be yellowish. The sore tongue and mouth may at first be the only signs, and they may persist for months or, it may be, for a year before complete sprue unfolds itself. The fiery red appearance of the tongue differentiates it from the "magenta tongue" of ariboflavinosis. Keele and Bound remark that the latter was never observed in tropical sprue cases in Burma.

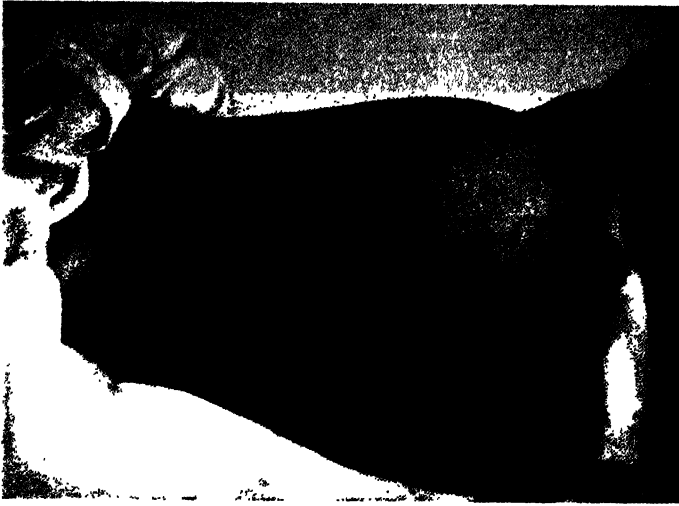


Fig. 96.—Sprue abdomen, showing intense meteorism in a Sinhalese. (P.H.M.B.)

Dyspepsia.—Dyspepsia is usually very troublesome, the feelings of weight, oppression, and gaseous distension after eating being sometimes excessive. Very likely the abdomen swells out like a drum, and unpleasant borborygmi roll through the bowel (Fig. 96). Occasionally, though not often, there may be vomiting, sometimes coming on suddenly, and not always accompanied by nausea. As a rule, there is a moderate hypochlorhydria, with adequate response to histamine, which may account for the dyspepsia.

Anæmia may be pronounced even in the early stages, though more generally it develops when diarrhœa has persisted for some time. It is a megalocytic, hyperchromic anæmia of the pernicious type, with alteration

in the size and shape of the erythrocytes, very occasionally with normoblasts. Occasionally, severe anæmia, indistinguishable from that of Addisonian anæmia, with high Van den Bergh readings, supervenes even when active sprue symptoms have disappeared.

Tetany associated with dilatation of the stomach is quite common in longstanding cases, but is also found in the early stages where there has been dehydration of the tissues and hypocalcæmia. It can often be elicited by compression of the upper arm (Trousseau's sign).

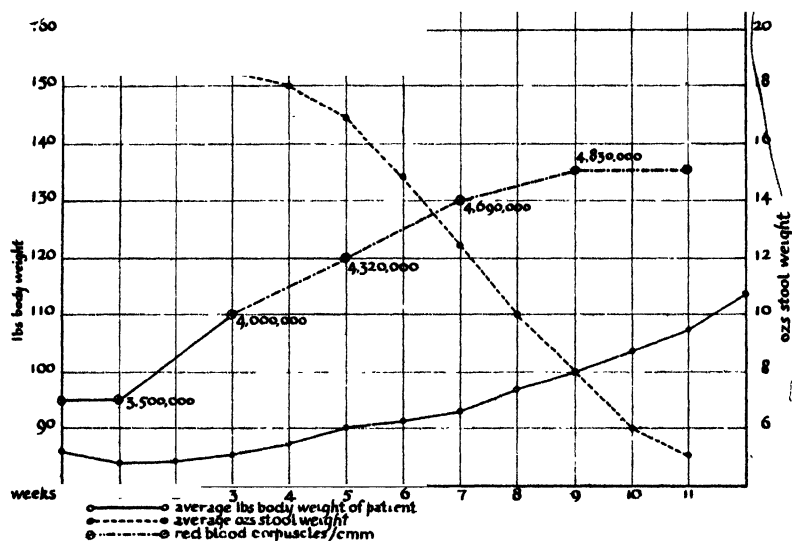


Chart 26.—Composite graph constructed from observations on ten cases, to show the relative increase in body-weight of patient and in red blood-corpuscles per cubic millimetre with coincident decrease in average weight of stool over the same period of treatment.

Cramps in hands and legs may be particularly distressing and are the accompaniments of hypocalcæmia.

Diarrhœa.—Diarrhœa associated with sprue is of two kinds: one chronic and habitual, the other more acute and, in the early stages, evanescent. The former is characterized by one or more daily discharges of a copious, pale, greyish, pasty, fermenting, acid, mawkish, evil-smelling material: the latter is watery, also pale and fermenting, the dejecta containing undigested food and, as a rule, an abnormally large amount of fat and fatty acids. In these latter circumstances diarrhœa usually brings with it considerable relief to the dyspeptic distension—at all events for a time. When the mouth is inflamed, diarrhœa is usually more active, but this is by no means invariable. The stools during periods of quiescence may be confined to one or two in the early morning or forenoon; during the later part of the day the patient is not disturbed. Even in this quiescent

phase, however, they are always extraordinarily copious, the excessive bulk being attributable in great measure to fatty acids and to innumerable microscopic gas-bubbles. They are passed almost, or altogether, without pain. Not infrequently during exacerbations there may be a tender, excoriated condition of the anus; and sometimes, in women, a similar condition of the vagina, causing pruritus.

Types, history, course and termination. *Primary or protopathic sprue.*—There is a striking uniformity in the history of most cases of sprue. The patient has probably been suffering for months, or perhaps for years, from irregularity of the bowels. This, the physician may be told, began soon after arrival in the tropics, as a bilious morning diarrhoea. For a long time this morning diarrhoea went on, without interfering in any way with the general health. Later; the mouth now and again became tender, little blisters or excoriations appearing for a day or two at a time about the tip of the tongue or inside the lips. These sore spots would come and go. Perhaps, from time to time, exacerbations of the mouth symptoms would be associated with a little increase of diarrhoea. Gradually, the stools lost their bilious character and became pale and frothy; dyspeptic symptoms, particularly distension after meals, now appeared. As time went on, these symptoms would recur more frequently, and in a more pronounced form, following, almost inevitably, any little imprudence in food or exposure. The general condition now began to deteriorate; emaciation, languor, lassitude, and inability to get through the day's work satisfactorily, becoming more pronounced each summer until, finally, a condition of permanent invalidism was established.

Should the disease continue to progress, the emaciation advances slowly but surely. Diarrhoea may be almost constant, and now no longer confined to the morning hours; the complexion becomes dark, sometimes very much so; the appetite, at first in abeyance, may be ravenous, unusual indulgence in food being followed by increased discomfort, temporarily relieved by smart diarrhoea. At length the patient is confined to the house, perhaps to bed. The feet become cedematous, and the integuments hang like an ill-fitting garment, the details of the bony anatomy showing distinctly through the dry, scurfy, earthy skin. Finally, the patient dies in a semi-choleraic attack; or from inanition; or from some intercurrent disease. Such is the history of an ordinary, mismanaged case of sprue.

Another type of case commences as an acute entero-colitis or "hill diarrhoea," with sudden and profuse colicky diarrhoea, perhaps vomiting, and a certain amount of fever. The acute symptoms do not subside completely, but gradually acquire those of sprue grafted on to those of acute intestinal catarrh.

Gastric cases.—Occasionally the morbid process is at first, judging from the existing clinical symptoms and subsequent history, confined to a limited part of the alimentary canal. Thus, there is sometimes sprue without diarrhoea, the principal symptoms being sore mouth, dyspeptic distension, pale, copious but solid stools, and wasting.

Intestinal cases are those with typical intestinal symptoms without involvement of the tongue or mouth.

Intestinal atrophy consequent on sprue.—In certain instances, under treatment the symptoms proper to sprue subside, but the patient's digestive and assimilative faculties are permanently impaired. Slight irregularities, either in the quality or the amount of food, chill, fatigue, depressing emotions, and other trifling causes suffice to bring on dyspepsia accompanied by flatulence and diarrhœa. These cases may linger for years. Usually, they improve during the summer in England, getting worse during the winter and spring, or during cold damp weather. Ultimately, the patients die from general atrophy, diarrhœa, or some intercurrent disease.

Secondary sprue.—Sprue may follow closely on the heels of some other severe intestinal disease, such as amœbic or bacillary dysentery, or may be the direct sequel of hill diarrhœa.

Sequelæ. *Anæmia and spinal symptoms.*—Severe anæmia of the pernicious type is a frequent sequel (see p. 511). Sclerosis of the spinal cord may occasionally ensue as in subacute combined degeneration in pernicious anæmia. Mild neuritic signs in the arms and legs (pins and needles) frequently supervene; sometimes also a generalized peripheral neuritis, with paræsthesia and loss of reflexes, resembling beriberi, which has been found to respond satisfactorily to vitamin B₁ therapy.

Edema.—Generalized œdema, especially of the legs, is a frequent accompaniment of sprue, especially in those patients who are responding to treatment, and is probably connected with salt depletion.

Purpura.—Petechial hæmorrhagic rashes, noticeable on the thighs and legs (Fig. 73, p. 418) are a scorbutic phenomenon and formerly occurred in patients who had been fed on milk. This rash disappeared after the administration of adequate amounts of vitamin C. Small subcutaneous hæmorrhages on the hands are common in atrophic cases of sprue and probably are scorbutic in nature.

Dermatitis.—A dermatitis is a frequent accompaniment of sprue, especially in elderly people with extreme anæmia. It generally breaks out during convalescence when the patient is responding to treatment, and is mostly seen on the arms and chest. Sometimes the rash is pellagrous, and the Editor has recorded cases of association of this disease with sprue, when improvement occurred on administration of nicotinic acid.

Special features of sprue in women.—Amenorrhœa and menstrual disturbances are extremely frequent in women with advanced sprue. Symptoms of sprue usually become exacerbated during pregnancy.

Relapses of sprue are unfortunately frequent and form a characteristic feature of this mysterious disease. Often they come on suddenly, and quite unexpectedly, without any apparent exciting cause. Sometimes the typical relapses are observed after an interval of twenty to twenty-seven years of apparently normal health in England.

Latency.—One of the most remarkable features of sprue is latency. Thus, it may arise in England in persons who have at some time resided in an endemic area of the disease. Usually, this period is one or two years; sometimes it is longer—seven or eight years; exceptionally it may be as long as twenty-five years.

Diagnosis.—The tongue, the stools, and the history seem sufficiently distinctive to render diagnosis easy. Cases do occur in which the disease has been diagnosed and treated as syphilis, the condition of the mouth being attributed to this disease, and the character of the stools and other symptoms ignored. Care must be taken in interpreting the significance of the smaller area of liver dullness usually found in well-marked cases of sprue. This is not due to cirrhosis of the liver, but to wasting, in common with other organs.

The chief basis of diagnosis of tropical sprue rests on the recognition of the very characteristic clinical appearance of the disease. This, of course, depends upon the experience of the observer. To the tropical specialist the "sprue facies" is quite distinctive. The bearing of the patient, his bedraggled and forlorn look impress themselves on one's observation. To those who have never seen tropical sprue before, the correct diagnosis is almost impossible. It is a matter of common experience that tropical sprue is often mistaken for carcinoma of the stomach, disease of the gall bladder—especially for cholecystitis.

Differential diagnosis.—*Celiac disease* (Gee's coeliac diarrhoea, or the Gee-Herter syndrome) occurs frequently in Europe in children under ten, and is also seen in those returning from the tropics. Coeliac disease is probably congenital and its ætiology is therefore different from that of sprue, but the stools are similar in appearance and in chemical composition. This disease is associated with diarrhoea and meteorism, stunted growth, and incomplete sexual development. There is no involvement of the tongue and mouth, and the anæmia is not so severe as in tropical sprue. Symptoms usually disappear on a gluten-free diet. *Idiopathic steatorrhœa* is probably the same process as coeliac disease persisting into adult life, and was described by Thaysen in Denmark and Northern Europe as *non-tropical sprue*. This is a nutritional disturbance associated with tetany, osteomalacia, osteoporosis¹ and anæmia. It is therefore characterized by disturbances of the calcium metabolism and anæmia, which is usually hypochromic, but may sometimes be hyperchromic and megalocytic. According to Bennett, Hunter and Vaughan, in "non-tropical sprue" there are often cutaneous lesions, infantilism, megacolon, fine silky hair, brittleness and ridging of the nails, clubbed fingers, and a flattened type of blood-sugar curve after ingestion of glucose (which is also found in tropical sprue). Lens opacities, gross bony deformities, and tetany constitute the outward signs of defective calcium metabolism. The serum calcium is low and there is excessive excretion of fat. Both coeliac disease and idiopathic steatorrhœa may be complicated by secondary pellagra. An important, almost diagnostic, point of differentiation, is that these two forms of steatorrhœa do not respond to liver and folic acid therapy as does tropical sprue, but to gluten-free diet.

The absence of skin lesions and mental symptoms differentiates sprue from pellagra, though tropical sprue may be complicated by secondary pellagra. Three instances of this association have occurred in the Editor's practice and have responded to nicotinic acid treatment. The sprue

¹ Osteoporosis has never been recorded in tropical sprue.

tongue may be difficult to differentiate from that of pellagra; the latter is pointed, and when it is inflamed and painful the process is generalized, not confined to certain definite and circumscribed areas as in sprue. The "magenta tongue" of ariboflavinosis is distinctive. The tongue of early pellagra (Plate XVIII) is usually associated with angular stomatitis and an atrophic condition of the lips (cheilosis). Atrophy of the lingual papillæ also occurs in pernicious anæmia and so this may be confused with sprue. No difficulty should be experienced in differentiating *Addison's disease* from sprue. *Gastro-jejuno-colic* fistula may give rise to symptoms simulating sprue, but these disappear when appropriate surgical measures have been undertaken.

Giardiasis (see p. 502) may produce light-coloured fatty diarrhœa, and may also be mistaken for tropical sprue.

Differentiation of sprue from *chronic pancreatitis* may present difficulties. In the latter condition neutral fats predominate in the fæces, the tongue and mouth are not involved, and the diastatic reaction of the urine is high.

The low blood-sugar curve after the intake of 1 grm. of glucose per kilo. body weight serves to differentiate sprue from pernicious and allied anæmias, but a similar curve accompanies idiopathic steatorrhœa and cœliac disease. The anæmia of sprue greatly resembles that of pernicious anæmia, though normoblasts are rare and megaloblasts do not occur. High van den Bergh readings are the rule in true pernicious anæmia: exceptional in sprue. Differentiation from tropical macrocytic or nutritional anæmia cannot be made on blood examination alone, as the picture is very similar. This anæmia affects pregnant women in the tropics, and is not accompanied by diarrhœa.

Certain cases of *tabes mesenterica* may, on clinical grounds, resemble sprue, and so may disease of the *mesenteric glands*, such as lymphosarcoma or lymphadenoma.

Whipple's disease, or intestinal lipodystrophy, must be considered in every case which bears some resemblance to tropical sprue. This syndrome is preceded by a migratory arthritis reminiscent of rheumatoid arthritis. A combination of the laboratory findings commonly associated with sprue may be present. The diagnostic criterion is based upon the microscopic findings in the peripheral lymph nodes (Casselman *et al*, 1954).

The radiographic findings in sprue.—The radiographic features are those of a deficiency pattern. Films should be taken at half-hourly intervals after a barium meal. Fluoroscopic examinations are made two or three times, usually with pressure films over the ileal region. Food is given five hours after the barium meal as soon as the barium has entered the cæcum. In early cases the mucosal folds of the small intestine may be reduced in number and appear more exaggerated, i.e., more irregular in width and spacing; but in advanced cases the mucosal folds may be entirely missing, giving rise to a smooth bag-like appearance or the "moulage sign." The mucosal changes are best seen in the jejunum.

Prognosis is good for recent cases, provided proper treatment is carried out. It is bad for patients over fifty, for longstanding cases, for careless and

injudicious patients, and for those who cannot or will not take a special diet.

Treatment

General statement.—The treatment of sprue is mainly a matter of bodily rest and careful dieting in order to procure assimilation of the most easily absorbable foods. If treatment be undertaken sufficiently early, and be thoroughly and intelligently carried out, it is generally successful. Should, however, it be undertaken too late, when the glands and the absorbing surface of the alimentary canal have been destroyed, the case is almost sure to end fatally. In prescribing treatment, therefore, the first thing is to get the patient thoroughly convinced of the serious nature of his complaint; for without his hearty and complete co-operation a well-established case will not be cured. To be successful, treatment must be thorough, sustained and prolonged. The average daily weight of normal faeces is from six to eight ounces; in sprue it is commonly double or treble this amount. By keeping a chart of the average daily excretion, and by estimating the weight of the food ingested, an estimate may be formed of the daily intake and output.

Nursing of sprue cases is all-important. A great deal rests with the nurse; sprue patients are apt to be unreasonable and refractory, so she will need to be sympathetic and tactful, yet firm. A regular routine of feeding should be strictly adhered to, both in quantity and ingredients. The sheet anchor of treatment in sprue is diet, as all who have written on this disease agree. Fats and starches are not well assimilated.

Specific treatment.—The discovery of folic acid (folvite) and its instantaneous and beneficial effect on the outstanding clinical signs and symptoms of sprue has raised the hopes that in this substance we have at last obtained a specific remedy in such a dire and puzzling disease. The scientific ground upon which this belief is founded is shown by its specific action upon the intestinal villi (Shiner, 1959). Folic acid treatment should be commenced directly the diagnosis has been established. In tropical sprue its first effect is upon the glossitis and mouth symptoms which remit within a few days and give almost instantaneous relief. The appetite improves and, with the abatement of diarrhoea and meteorism, there ensues a sense of well-being and a desire for food. In some patients this follows in a few days and they commence to regain the weight lost. It would appear that the larger doses of folic acid which were first considered advisable are not necessarily essential. The curative dose ranges about 30 mgm. daily and the maintenance dose from 5–10 mgm. Folic acid treatment should be instituted directly the diagnosis has been arrived at, whether the patient is in the early or late stage of the disease.

The following doses are suggested:—30 mgm. daily for 10 days; 20 mgm. for a further 10 days—thereafter 5 mgm. daily as maintenance dose.

In order to obtain the maximum hæmatological response folic acid must be combined with intensive intramuscular liver therapy. Spies and colleagues have found that a compound—5 methyl uracil, or thymine—can be substituted for folic acid, but large doses are necessary, i.e., about 6 grm. daily for 14 days as compared with 20 mgm. of folic acid.

Recent researches by French, Gaddie and others (1956) have a definite bearing on the principles of treatment as well as upon the ætiology of tropical sprue. They found that if early, uncomplicated cases in young men were treated intensively with sulphonamides (sulphasuccidine, sulphathalidine) or with antibiotics (chloramphenicol, chlortetracycline, streptomycin or penicillin) improvement rapidly took place, resulting in a rapid return to normal of fat absorption. Progress was determined by general examination and by daily faecal fat determinations, by chylomicrographs and glucose tolerance tests. Body weight increased rapidly and glucose tolerance tests improved. At the end of the course of chemotherapy the colour of the faeces changed from pale to dark and had become formed.

This seemed to indicate that chemotherapy had counteracted some infective agent and at the same time had restored the absorptive capacity of the bowel.

Treatment of anæmia.—In extreme cases with blood destruction in which the blood picture resembles that of advanced pernicious anæmia blood-transfusion is essential and some with a red cell count of half a million r.b.c. per c.mm. have recovered. Sometimes two or three transfusions at weekly intervals are advisable.

The beneficial effects of liver soup in sprue have been noted since the early days of Manson and van der Burg. The best preparations of liver suitable for oral administration are those of Eli Lilly, Parke Davis, and Oxo (Liveroid), but large quantities are required, and they are expensive. An important advance is intramuscular injection. *Hepatex*, *Plexan* and *Examen* are most efficient. In grave cases 4 ml. is injected daily for six injections, but usually a series of 12 injections of 2 ml. suffices. They should be made deep subcutaneously into the buttock, and are usually followed on the ninth or tenth day by a rise in the reticulocyte count. The first injections may be rather painful, but this gradually works off as more are given. Sometimes the addition of iron is of advantage, especially in cases without megalocytic blood changes. It may be given in the form of ferrous sulphate tablets (Glaxo) three times daily, or of *Hæmatinic plastules* (Wyeth).

Cytamen or vitamin B₁₂ (*Injectio cyanocobalamine* B.P.C.) in sterile solution containing $\frac{1}{3240}$ gr. in 15 min. (20 µg. in 1 ml.) injected intramuscularly twice weekly is indicated in those cases which do not respond satisfactorily to liver therapy.

Other vitamins.—Some cases of sprue with angular stomatitis improve on liberal administration of vitamins, such as riboflavin, but if there are other evidences of vitamin deficiency a combination of vitamins is indicated such as *Beplex* (Wyeth) which contains aneurin, riboflavin, nicotinic acid, pyridoxin, and pantothenic acid.

Diet.—Much has been written about the details of a sprue dietary and most varied opinions have been expressed. When the tongue and mouth are very sore the patient is fed on milk, and should this not be well tolerated on Sprulac (p. 521). Horlick's and Benger's preparations are also suitable. A high protein dietary, as advocated for pernicious anæmia, is preferred by some authorities. In the second week the patient may be allowed three

pints of milk daily, with rusks or toast, a lightly boiled egg, minced chicken, sweetbreads, minced liver, semolina, ground rice and tapioca puddings. Junket is also suitable. Amongst fruits, bananas and baked apples are well tolerated. Formerly mystical properties were attributed to strawberries in the treatment of sprue.

The principle of sprue dietary is avoidance of fatty or greasy foods and the ingestion of too much carbohydrate.

In elderly patients (*i.e.*, those over 45) and where there is a high degree of anæmia, the addition of raw or underdone, finely shredded beef is of advantage.

Minced beef for Sprue Patients

8 oz. best beef ;
1 good teaspoonful of marmite ;
Pepper and salt ;
2-3 tablespoonfuls of water.

Trim off all fat from the beef. Mince the raw beef finely, putting it twice through the mincing machine if necessary.

Place in double saucepan with marmite, seasoning, and water. Cook over boiling water, *stirring the ingredients with a fork all the time* until the meat has turned *brown and crumbly*—roughly 3 minutes.

Serve on a hot-water plate. Treated in this manner minced beef is a palatable dish.

Lightly-steamed meat with gravy is advantageous, and should be steamed in the following manner :

Take undercut of beef, 4 oz. Steam with 6 oz. of water for 5 to 7 minutes. Add a pinch of salt and serve as thick soup with lemon juice or slice of tomato.

The recipe for liver soup is as follows :

Take half a pound of calves' liver and cut it into small pieces. Place in a double saucepan, add $\frac{1}{2}$ pint of cold water and simmer for $1\frac{1}{2}$ hours. Strain through a sieve and add 1 pint of bone stock or chicken jelly, and, if necessary, flavour with marmite. Add a small quantity of pepper and salt.

Liver soup can be given in soup-platefuls of 8 oz. each, and may be taken together with underdone meat.

Food should never be given unless the patient is hungry. It is a great mistake to try to let these patients eat quickly, or to stimulate the desire for food by encouraging active exercise. The bowel is not in a condition to deal with large meals.

A high-protein milk powder, or *Sprulac* (Cow & Gate, Ltd.) is prepared from fresh milk which has been treated by passage through a gauze and wire filter, subsequently chilled, centrifuged to get rid of organic and inorganic débris, passed through a mechanical mixing apparatus and eventually desiccated at 120° C. The powder contains 10.6 per cent. fat ; 34.0 per cent. protein and 45.0 per cent. lactose. The calorie value per ounce is 125 and the ratio of protein, fat and carbohydrate is 1.0 : 0.3 : 1.3. *Sprulac* can be given in the same manner as milk. One ounce of *Sprulac* is made up to 8 oz. with water and given every $2\frac{1}{2}$ hours for six feeds. Subsequently the amount may be increased and calves'-foot jelly and the juice of two oranges added. *Sprulac* forms an excellent addition to the diet in all stages of sprue.

Dehydration.—Dehydrated cases must be treated on modern lines with fluid replacement therapy by intravenous drip saline. Treatment by increasing the salt intake to 15 grm. daily combats the dehydration, usually in a few days. Checking the diarrhœa by the use of sulphasuccidine is most important.

Return to Europe.—When sprue develops in the tropics, if feasible, the patient should be sent to Europe as soon as possible. It is a mistake, however, to ship an invalid if the disease is active, or the end manifestly not far off. Diarrhœa should not be present when the patient is put on board ship. The effect of folic acid in a hot climate appears to be equal to that observed in Europe, and this necessarily has exerted a considerable influence on the management of this disease in the tropics.

Clothing and general management.—Sprue patients returning to Europe ought to be especially careful in their clothing, and they ought to get out their warm clothes before the ship leaves the tropics.

During the summer England is suitable enough as a residence; but during the cold winter and spring months some milder, drier and more sunny climate must be sought.

Sore tongue and mouth.—This responds readily to folic acid treatment, but a great deal can be done to ameliorate the soreness and the dysphagia caused by ulceration of the tongue and mouth. The mouth should be kept very clean and washed out after each feed with a bland mouth-wash such as potassium chlorate, 1 drachm to the pint of hot water, but if the mouth is very painful, cocaine, 2 gr. to the ounce of glycerin and borax, brushed on to the tongue lightly before eating, will deaden sensibility. In certain cases where the saliva is very acid, as it generally is when the tongue is very raw, an alkaline mouth-wash should be used as follows:

Sod. bicarb.	gr.x (0.648 grm.)
Sod. biborate	gr.x (0.648 grm.)
Rose-water	℥iv (113.6 c.c.)
Diluted with water according to taste.		

Diarrhœa.—The diarrhœa of sprue usually yields to dietetic treatment. If nocturnal diarrhœa is very severe, *chlorodyne* (10–15 min.) is often successful. Sulphonamides, especially sulphasuccidine, in full doses of 5–10 grm. daily, according to the patient's weight and tolerance have proved very successful in checking sprue diarrhœa. Recently a course of aureomycin capsules (0.25 grm.), four daily for four days, has been strongly recommended.

Anal excoriation and irritation is sometimes a distressing feature, and may be relieved by the following ointment:

Orthoform	40 gr.
Zinc oxide	120 gr.
Starch	120 gr.
Paraffin	ad 1 oz.

Tetany and cramps.—The treatment of these symptoms, which are due to calcium deficiency, is by administration of calcium by the mouth in doses of 10 gr. three times daily, and in extreme cases by intravenous injection of salts, such as calcium gluconate (Sandoz) 10 ml. or over.

Convalescence.—Sprue patients, if possible, ought not to return to the tropics. Young adults often recover completely, but the danger of relapse is greatly enhanced in those over 50 if they return to a hot country, especially India. If compelled by circumstances to do so, they must exercise the utmost care for their health, and avoid exposure, cold baths, and all excesses; purge gently, and go on simple diet on the slightest sign of relapse. Alcohol, especially strong spirits, is strictly contra-indicated for at least three months from the time of apparent recovery. A maintenance dose of 5 mgm. folic acid daily is recommended.

HILL DIARRHŒA

Little has been heard in recent years about hill diarrhœa. It is a form of morning diarrhœa accompanied by flatulent dyspepsia and the passage of copious liquid, pale, frothy stools. It occurs principally in Europeans on visiting the hills after residing for some time in the hot lowlands of tropical countries. Hill diarrhœa is a frequent precursor of the fully developed disease—tropical sprue—and probably is of similar ætiology.

Crombie, who gave an excellent account of this disease in India, pointed out that a similar affection may show itself in the highlands of Europe, Africa, and possibly South America, and Steen described a similar diarrhœa in Java, where it is known as “Bandoeng sprue.” There is no reason, therefore, to suppose that hill diarrhœa is peculiar to India, although, owing to the large European population frequenting the hill sanatoria in that country, it has been particularly noticed there. An elevation of 6,000 feet or over, when combined with an atmosphere saturated with water vapour, is particularly favourable to its development. In India it is found to begin and end with the rains, during which, in certain years and places, it is apt to assume almost epidemic characters. In some years hill diarrhœa is less prevalent than in others; but at the proper season few of the various hill sanatoria of India are without cases.

Without very obvious cause, the patient, who in other respects may be in good health, soon after arrival at a hill sanatorium becomes subject to a daily recurring diarrhœa, the looseness coming on regularly every morning some time between 3 and 5 o'clock. The calls to stool are apt to be sudden and imperative. The motions passed are remarkably copious; very watery in some instances, pasty in others. They are pale, frothy, and like recently stirred whitewash, so devoid are they of biliary colouring matter. Their passage is attended with little or no pain, often with a sense of relief. From one to half a dozen, or more, such stools may be voided before 11 a.m. After that hour—at all events, in ordinary cases—the diarrhœa is in abeyance for the rest of the day, and the patient may go about his duties or pleasures without fear of inconvenience.

Treatment.—In view of the discovery of folic acid the older ideas of treatment will have to be revised. The diarrhœa generally yields to strict diet—milk and junket, warm clothing and removal to a lower altitude. The diarrhœa is checked with sulphasuccidine in full doses as well as the administration of folic acid.

Section IV.—INFECTIVE GRANULOMATOUS DISEASES

CHAPTER XXXIV

LEPROSY

Synonyms.—Hansen's Disease; Hansen's Infection; Elephantiasis Græcorum.

Definition.—A chronic contagious granulomatous disease due to infection by *Mycobacterium lepræ*. The tissues principally affected are the skin and peripheral nerves, but in some cases there is spread to other tissues such as the reticulo-endothelial system, the mucosa of the mouth and upper respiratory tract, the eyes, bones and testes.

Epidemiology.—Geographical Distribution: The world incidence of leprosy is conjectural owing to the fact that few countries have accurate records of the disease, but it is generally believed to be in the region of ten millions. The greatest incidence is in the tropics and subtropics, but it is by no means confined to these regions. Figures for 1952, published by the American Geographical Society, show that the highest endemicity occurs in Africa where *known* cases number 14·5 per thousand in Basutoland, 6·8 in French Equatorial Africa, 6 in Belgian Congo and 4 in Nigeria. The highest estimated incidence is in Belgian Congo (16·7 per thousand). Leprosy in Western Europe is confined to immigrants, but it remains an endemic disease in Southern and South-Eastern Europe with 1,416 known cases in Portugal, 1,708 in Spain, 364 in Italy, 887 in Greece, 109 in Malta 98 in Cyprus and 4,000 in Rumania. According to del Vecchio (1955), leprosy is on the increase in Italy. It appears to be dying out in Northern Europe with only 11 known cases in Norway, 6 in Sweden, 9 in Finland, and a little over 100 in the Baltic States. The U.S.S.R. has 3,000 known cases, the U.S.A. has 890 (mostly among immigrants), Cuba has 2,840, Mexico has 8,000, Brazil has 61,191, India has 140,000, Ceylon has 8,959. There are a few lepers in Iceland. The disease is spreading in Brazil, in Dutch New Guinea, amongst the Australian aborigines, the Solomon Islanders and also in some other Pacific Islands

Incubation Period.—This is not known precisely but is usually between one and two years. An incubation period of only five months has been recorded in an infant by Dreisbach (1954), but little reliance can be placed on reports of long incubation periods as early signs of the disease may be overlooked for years.

Age and Sex.—Leprosy can be contracted at any age and by either sex, but infants and children are more susceptible than adults. Most statistics show that the incidence is higher in men than in women, but this is probably due to the fact that the latter in the tropics tend to avoid doctors and hospitals. It is significant that Hopkins and Faget found no disparity

in Negro admissions to the United States Marine Hospital at Carville over a studied period, and there is universal agreement that children are affected equally.

Factors influencing the spread of the Disease.—For a long time the view was firmly held that leprosy was a hereditary disease, and from time to time various theories were propounded regarding the dangers of certain foods, but these views have not stood the test of time. That leprosy is more common in regions where food is inadequate is probably due to the fact that poor diet usually goes with poverty and bad living conditions.

It is now generally accepted that the most important factors influencing the prevalence of leprosy are a low stage of civilization and accompanying grave hygienic defects such as defective housing and over-crowding. These provide ideal conditions for the spread of leprosy within the family and the community. Where hygienic conditions are favourable there is little or no tendency for the disease to spread, and this was shown by Hansen's observations in 170 Norwegians who migrated to Minnesota, U.S.A., when suffering from leprosy. Not one of their descendants contracted the disease in America.

Among other factors in the spread of leprosy are promiscuity and the prevalent habit in the Pacific Islands of smoking communal pipes, and of eating out of the same dish, and also the universal tendency for children to romp and wrestle with each other. Domestic servants and children's "nannies" are rarely subjected to a medical examination prior to, and during employment, and so may infect members of the household.

In addition to hygienic living conditions there may be other factors at work limiting the spread of leprosy. Chaussinand (1948) has put forward the theory that leprosy is less likely to spread in a community which has developed a high level of immunity to tuberculosis. Other factors, not yet understood, are probably at work making for individual immunity, thus explaining why leprosy may not develop in one adult who is repeatedly at risk while it attacks another adult of the same race and social background who had minimal contact with the disease.

Epidemic diseases such as typhus and plague, attended by a high mortality rate, have in the past resulted in great, though usually temporary, decline in the prevalence of leprosy. Some medical historians hold the view that the decline of leprosy in Europe in the 14th and 15th centuries was largely due to the plague pandemics then raging.

Ætiology.—From the foregoing remarks it will be seen that leprosy is conveyed from the sick to the healthy by contact and that child contacts are more susceptible than adults. This does not mean that adults are not capable of becoming infected. On the contrary, there are numerous records of adults taking up residence in a country where leprosy is endemic and of acquiring the disease. Furthermore, such persons may carry the disease back to their own country when they return and can communicate it to their fellow countrymen. One instance of this was recorded by Benson (1887) when an Irish soldier returned to Dublin from the tropics and infected his brother who had never been out of Ireland. It should be

noted that the patient and his brother were in the habit of sharing the same bed. The Editor studied a somewhat similar case in a woman whose husband—a Mauritian—had died of leprosy, and who developed the disease in London where she had lived all her life, after an incubation period of seven years.

The precise method of transmission has not been proved, but is thought to be via the skin, whether broken or unbroken, as a result of direct contact. So far all attempts to infect human volunteers have, with two doubtful exceptions, failed. Arning claimed to have succeeded in an experiment to infect a Hawaiian named Keanu, but this volunteer was later found to have a strong family history of leprosy; and a doctor working in Egypt, named Lagoudaky, who received blood intramuscularly and intravenously from two leprosy patients, developed a disease which was thought to be leprosy but was never proved bacteriologically or histologically.

Evidence of accidental transmission by injection has been produced by de Langen (1936) who reported the case of a European in Java who was injected with morphine from a syringe previously used on a leprosy patient; six months later a leprosy nodule appeared on the arm at the exact site of the injection, and subsequently other signs of the disease were noted. Porrit and Olsen (1947) reported on two American marines who developed tuberculoid leprosy in the tattoos they had received on the same day and in the same shop when they were in Australia; Rogers and Muir (1946) quote four reports on doctors who became infected through wounds to their fingers while operating, and they also describe the case of a barber who developed tuberculoid leprosy on the area of his forearm which he always used for stropping his razor. One form of diet said to predispose to leprotic infection is the edible root *Colocasia* in the Pacific Islands.

The leprosy bacillus was discovered in Norway by Hansen in 1873 and the work was published in 1874 when he described the "rod-shaped bodies" which he had found in leprosy nodules. Five years later (in 1879) a detailed description of *M. lepræ* was published by the German bacteriologist, Neisser.

Bacillus lepræ (*Mycobacterium lepræ*).—This organism is now the accepted cause of leprosy and is present usually in great profusion in the tissues. In size, shape and staining reactions it closely resembles the tubercle bacillus. It exhibits marked pleomorphism; the ends are somewhat attenuated. Individual bacilli vary in size, from 1.5 to 5 μ in length and from 0.2 to 0.5 μ in breadth. Curved forms with pointed ends are not uncommon. In the reactionary stages of the disease the organisms may be granular, coccoid, mono- or bipolar. Round, spore-like bodies often impart a granular appearance to a clump of bacilli. In common with the tubercle and smegma bacilli *Myco. lepræ* is acid-fast, retaining carbol fuchsin stain after being treated with mineral acids, though it may be distinguished from *Myco. tuberculosis* by being more easily decolorized by alcohol than by weak acids. Moreover, it occurs in large numbers in the lesions, chiefly in zooglycea masses within the lepra cells, often grouped together like bundles of cigars or arranged in a palisade. Chains are never

seen. Most striking are the intracellular and extracellular masses, known as *globi*, which consist of clumps of bacilli in capsular material. (Fig. 97.)

Under the electron microscope the bacillus appears to have a great variety of forms (Brieger and Glauert, 1956). The commonest is a slightly curved filament 8 to 10 μ in length containing irregular arrangements of dense material sometimes in the shape of rods. Short rod-shaped structures can also be seen (identical with the rod-shaped inclusions within the filaments) and also dense spherical forms. Some of the groups of bacilli can be seen to have a limiting membrane. In a study of leprosy during treatment by the same methods, Malfatti and Jonquieres found the peripheral envelopes surrounding the isolated units and globi tend to disappear as their vitality and virulence become less. This permits direct contact with the bacilli and production of natural antibodies.

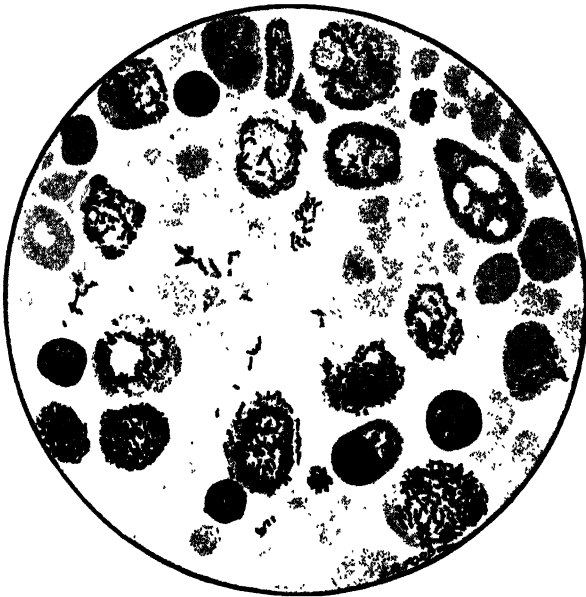


Fig. 97.—Section of spleen showing lepra cells and lepra bacilli.
× 800.

Cultivation of Myco. leprae, though repeatedly attempted, has never been really successful. Some investigators, it is true, have obtained growths of acid-fast bacilli (chromogenic and non-chromogenic), or diphtheroids, which in some instances have developed acid-fast forms on subculture. Others have described branching bacilli, granular and coccoid forms.

Freire (1956), in New Orleans, claims to have successfully grown *M. leprae* and to have subcultured it 15 times. He used Kirchner's medium with the addition of 1 per cent. agar and 20 per cent. human serum. Serum from a lepromatous patient was used for primary isolation and normal serum for the subcultures.

Three methods were used: a slide culture technique in which the organisms are fixed by immersion in 6 per cent. sulphuric acid; a modification of a small tube, and direct inoculation into the medium. Only the last method was used for the subcultures.

Five isolations were made in 17 attempts with material from 12 lepromatous patients. Importance is attached to the formation of globi in the primary culture.

Animal inoculation of leprosy.—K. R. Chatterjee (1958), at the Calcutta School of Tropical Medicine, has succeeded in inoculating *M. lepræ* into hybrid mice (a cross between the Swiss white mouse and the common Indian house-mouse). Typical lesions develop after six months and the contained bacilli have satisfied all tests for *Mycobacterium lepræ*.

It is probable that all four varieties (diphtheroid, pigmented acid-fast, apigmented acid-fast and acid-fast streptothrices) have been more or less commonly encountered in leprous tissue in various parts of the world. When some of these cultures are injected, transient granulomatous lesions have been obtained, but there is general agreement that they do not constitute true leprotic lesions.

Inoculation of animals with human leprous material containing prodigious numbers of organisms does not give rise to typical progressive leprous lesions. Adler (1937) succeeded, to a limited extent, in communicating leprosy to young splenectomized Syrian hamsters (*Cricetus auratus*). A fragment of lepra nodule was inserted under the skin and, when the animal was later killed, leprosy bacilli were demonstrated in the liver, and (in other animals) in neighbouring enlarged and caseating glands, but he failed entirely to carry on the disease by subinoculation in a continuous series of hamsters. Similar results have been obtained by Burnet. Subsequently Dharinendra and Lowe in India, in a series of carefully planned experiments on the same animals, by implantation into the abdominal wall and intraperitoneal inoculation, failed to produce generalized or progressive infection. When the nodule was implanted into the abdominal wall, masses of bacilli were found at the site of the implant, but not beyond, and bacilli were found elsewhere in two animals only. The fact seems to be that lepra bacilli can survive for long periods in inoculated animals, even dead bacilli may evoke local reactions and produce pathological appearances similar to those produced by living organisms. Araujo, in Brazil, appears to have had experiences similar to those of Adler and to have found the organisms in the European hamster (*Cricetus cricetus*) in great profusion. Collier (1940) implanted lepromatous material beneath the skin of monkeys fed on a diet of *Colocasia* (Yam) over a long period. It is claimed that some developed symptoms reminiscent of leprosy in man and that acid-fast bacilli were obtained from material procured from the ears of these animals. Cochrane, Menon and Pandit, on repeated injections of splenectomized monkeys with human leprosy material, found that they developed strongly positive lepromin reactions. Cochrane considers that *M. lepræ* cannot parasitize the reticulo-endothelial system, unless it multiplies in the corium of the skin. Hanks attempted to cultivate leprosy bacilli in small cubes of leprous tissue placed in various fluid and solid culture media, as well as by injection of leprosy material into chick

embryos and chick tissue cultures. No evidence of proliferation of the bacilli was obtained.

Rat leprosy.—A leprotic disease of the rat, which occurs naturally throughout the world, was first observed by Stéfansky in Odessa in 1903. Two types are recognized: disease of skin and muscle and disease of lymphatic glands. In tropical rats it occurs commonly and has been specially studied by Lampe and de Moor in Java. House rats are usually affected, especially *R. rattus concolor* and *R. decumanus*. Infection in these animals is conveyed by injury and by cannibalism. Laidlaw succeeded in transmitting this disease to the Syrian hamster, and it can also be conveyed to rats of the same species, infection taking place readily through skin abrasions and subcutaneous inoculation. The bacillus is *Mycobacterium lepræ murium*, morphologically indistinguishable from *Myc. lepræ*, whilst the lesions resemble those of human leprosy, macroscopically as well as histologically. Attempts at cultivation have shown much the same negative results as in human *Myc. lepræ*.

Fielding has demonstrated numbers of bacilli in the urine and fæces of rats, and has proved that ancylostome larvæ can take up these organisms from the fæces and introduce them into the skin. Repeated inunction of the healthy skin will, moreover, produce infection.

In spite of the general similarity of human and rat leprosy, it is generally agreed that the organisms represent two separate and distinct species and there does not seem to be any connection between this disease of the rat and human leprosy.

Pathology.—The observations of Khanolkar (1951) support the view put forward by certain earlier observers that the usual method of infection is by direct contact, leprosy bacilli being transferred from infected skin to the unbroken skin of a healthy person by a process of "rubbing-in." Khanolkar has confirmed the forgotten studies of German pathologists half a century ago on the neural spread of the infection, and has beautifully demonstrated that the bacilli enter the finest nerve twigs in the superficial nerve plexuses of the dermis and travel along sensory and sympathetic nerves within their axons in a centripetal direction. Their subsequent progress may be confined solely to nerves or may be punctuated by periodic bursting out of bacilli into the dermis. The effect on nerves and skin depends on the infected individual's defence mechanism and in particular to the type of cellular reaction. A good defence mechanism results in a tuberculoid histological picture, whereas an inability of the tissues to mobilise an effective response leads to lepromatous leprosy. A partial or unstable tissue response is characteristic of the intermediate forms of the disease.

In tuberculoid leprosy there is an active cellular reaction in the invaded tissues characterized by an inflammatory exudate of lymphocytes, epithelioid cells and Langhans-type giant cells. In the skin, these cells are collected in foci in relation to skin appendages, the giant cells and epithelioid cells in the centre and the lymphocytes ranged around them. Some of these granulomatous foci involve the papillary zone of the skin and thus extend right up to the epidermis. Bacilli are scanty or absent.

Cutaneous nerve twigs show cellular infiltration which later leads to degeneration, and the nerve filaments encircling the hair shafts are destroyed earliest of all; larger nerves may actually undergo caseation. This type of active cellular defence is able to prevent the spread of the infection to tissues other than skin and nerves, and may even be successful in arresting the infection if untreated. Certain tissues may be affected secondarily as a result of nerve damage, particularly muscles and bones.

In **lepromatous leprosy** the cellular reaction is passive rather than active, and although large numbers of mononuclear cells (histiocytes) become massed at the sites of infection in the skin, they fail to destroy the bacilli or to anchor the infection. In fact, bacilli become disseminated to other parts of the skin via tissue fluids and lymph, to other parts of the peripheral nervous system via axonal pathways, and to distant organs via lymph and blood (Fig. 98).

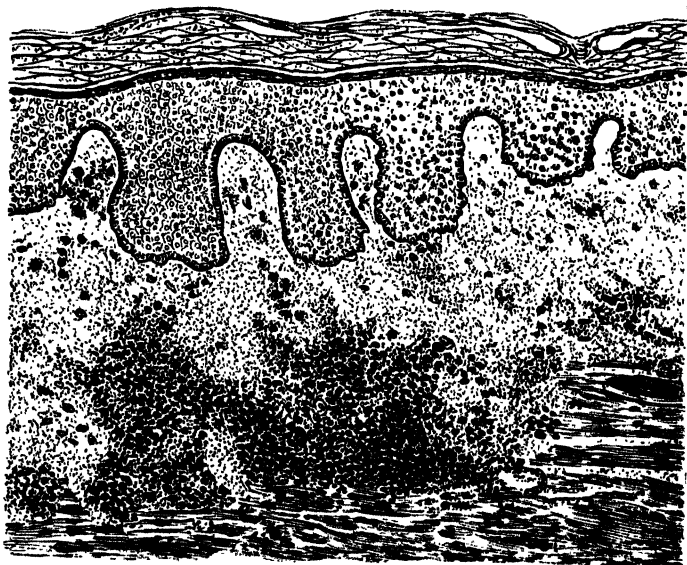


Fig. 98.—Early lepromatous lesion, showing diffuse infiltration of sub-papillary, and dense infiltration of sub-epidermal layers.

Thus a section of a skin lesion in lepromatous leprosy shows a dense collection of vacuolated cells in different stages of development from mononuclear cells to typical foam cells of Virchow (macrophage cells). Lymphocytes and plasma cells may also be present. Enormous numbers of bacilli can be demonstrated, some lying singly and others packed within greatly swollen macrophages (globi) or in smaller groups. The granulomatous process, unlike that in tuberculoid leprosy, is diffuse and leaves a clear zone immediately beneath the epidermis; nerve filaments stand out clearly and are invaded by bacilli, but there is no cellular infiltration within the nerves and there is no structural damage. Larger nerves, however,

may suffer damage due to œdema, which in turn leads to anoxia owing to the limited expansile capacity of the surrounding nerve sheath (epineurium). Anoxia gives rise to fibrosis, and a nerve section at this stage shows degenerate nerve fibres and considerable fibrosis in the perineurium and epineurium, the general architecture of the nerve being maintained. This appearance is very different from the complete intra-neural disorganization seen in tuberculoid leprosy.

Invasion by bacilli and macrophage cells takes place in other tissues besides skin and nerves, namely: mucosa of mouth, pharynx and upper respiratory tract; reticulo-endothelial system; eyes; testes; and bones.

Mucosal involvement leads to swelling and ulceration which is most serious if it affects the larynx, and ulceration of the nasal septum may result in destruction of cartilage and saddle-nose deformity. The mucosa of the trachea may be involved, but the lungs and bronchi escape.

Reticulo-endothelial involvement takes the form of lymphadenopathy and of bacillary invasion of the reticulo-endothelial elements in the red marrow and in the liver, spleen and other abdominal viscera. The glands most commonly enlarged are the inguinal, femoral and epitrochlear glands, and on section they have an unmistakable yellow or yellowish-brown colour. In the liver the bacilli are found in swollen Kupffer cells, in the interlobular connective tissue and around the central veins, while in the spleen the bacilli invade the Malpighian bodies and the arterial sheaths. Small numbers of bacilli have been demonstrated in the œsophagus, stomach and intestine, with involvement of corresponding lymph glands, but intestinal ulceration does not occur. In the kidneys the presence of bacilli in the glomeruli may cause hyaline degeneration and interstitial nephritis. As the duration and the extent of the lepromatous disease increases, the patient is likely to develop secondary amyloidosis of the alimentary canal, liver, spleen, kidneys and adrenal glands. Proteinuria (without hæmaturia) and anæmia are signs which herald the onset of this serious complication, and the Congo red test will be positive in a well-established case.

Testicular damage takes the form of tubular atrophy which may progress to complete tubular fibrosis and obliterative endarteritis, by producing a syndrome simulating the Klinefelter syndrome (1942) characterized by azoospermia and increase of the follicle-stimulating hormone of the anterior pituitary (F.S.H.) in the urine. Where there is damage to the interstitial cells of the testis, in addition to tubular damage, secretion of androgens is impaired with resulting impotence, gynæcomastia, osteoporosis and diminished urinary output of 17-ketosteroids.

The *bones* may suffer as a result of four factors—deposits of bacilli in the medullary cavities and in the periosteum; nerve damage producing neurotrophic bone changes; loss of pain sensation in the skin leading to repeated trauma; trophic ulceration resulting in septic necrosis of bone.

The *eyes* may show evidence of keratitis and iritis.

In *borderline (dimorphous) leprosy* the cellular reaction is dimorphous in that it has characteristics of the two types of leprosy, tuberculoid and lepromatous, and is therefore typical of neither. In the skin it usually consists of lymphocytes, mononuclears and epithelioid cells, tends to be focal in distribution and to leave a narrow but clear zone immediately

beneath the epidermis. Bacilli are usually found in small or moderate numbers, and are also present in nerves accompanied by lymphocytes and epithelioid cells. Tissues other than nerves and skin are not affected unless the disease is advancing towards the lepromatous type.

In **indeterminate leprosy** the cellular reaction, which is confined to skin and nerves, is of simple inflammatory type and is not characteristic of leprosy. This is generally considered to be an unstable stage of leprosy occurring in a proportion of patients prior to the development of features typical of lepromatous, tuberculoid or dimorphous leprosy.

Laboratory Tests.—These are of significance only in lepromatous leprosy or in dimorphous leprosy which is close to the lepromatous type, and the principal abnormalities are as follows:—

Blood Count.—Anæmia is commonly observed in advanced disease and may be due to several factors. If parasitic and nutritional disorders can be excluded, together with toxic effects of anti-leprosy drugs, one must consider ætiological factors such as amyloidosis, chronic sepsis, and marrow dysfunction due to invasion by bacilli and macrophages.

Erythrocyte Sedimentation Rate.—This may be raised, especially during reactive phases.

Liver Function Tests.—Abnormal results in tests of liver function are commonly found, even in the absence of any symptoms of hepatic dysfunction: e.g. thymol turbidity above 4; reduction in serum albumin and increase in serum globulin, particularly in gamma globulin.

Serological Tests for Syphilis.—When certain of these tests are carried out, the best-known being the Wassermann reaction and the Kahn test, approximately one-half to two-thirds of all lepromatous patients give false positive results, particularly when employing complement-fixation tests with cardiolipin-lecithin antigens (Edmundson *et al.*, 1954). There appears to be no correlation between seroactivity and the levels of the serum proteins or the number of leprosy bacilli in the tissues. Treponemal infection can be excluded if the T.P.I. (treponemal immobilization test of Nelson and Mayer, 1949) is negative.

Other Tests.—The Middlebrook-Dubos hæmagglutination reaction (1948) gives a positive result in a high proportion of cases, but there is doubt regarding the value of this test in leprosy.

The bacilli can be readily demonstrated by excision of a leproma, or they can be obtained by clamping a nodule with a specially-constructed, narrow intestinal clamp, pricking the solid tumour, collecting a droplet of expressed "leper juice" on a coverslip and staining by the Ziehl-Neelsen method. They are Gram-positive. They are found in all primary deposits, in the skin lepromata, in marginal infiltration of the macular eruptions (where they may be very sparse), in apparently normal skin in the vicinity of leprous lesions, in the early stages of leprous neuritis (where also they may be present in small numbers) and in the specific lesions in the liver, spleen, testes and lymphatic glands. In the blood vessels they have been found in the endothelium and occasionally free in the blood, or engulfed by leucocytes. This fact is specially useful in diagnosis when thick de hæmoglobinized blood-films are stained by Ziehl-Neelsen stain. Bacilli are also abundant in the purulent and mucoid

discharges from the nose, as well as from ulcerating lepromata. Very rarely have they been found in the spinal cord or lungs.

When the resistance of the individual is high, characteristic histological changes are: concentration of round cells, especially round hair follicles and vessels and development of the "tuberculoid focus," similar to tuberculosis. The essentials in the histology of the skin in resistant or neural leprosy are: localization of the process in the skin, the foci being chiefly perifollicular and perivascular; formation of epithelioid and giant cells; invasion of the cutaneous nerves.

The histopathology of the nerve lesion corresponds to that of the skin. In advanced lepromata bacilli and lepra cells are more abundant and there is formation of fine fibrous tissue in the endoneurium which may later contract and block the nerve-fibres. In the neural type bacilli are few, though it is easier to find them in nerves than in the skin. The cellular reaction also tends to be more intense, so that epithelioid and giant cells are present in greater or lesser numbers surrounded by small round cells. Thickened nerve trunks may become enclosed in a dense fibrous sheath which may later cause constriction.

In the non-resistant case the essential cell is the macrophage but, as the bacilli multiply, so no attempt is made to localize infection, owing to the relatively lowered resistance of the tissues. The bacilli multiply rapidly, the macrophages become active and phagocytose the bacilli. These are the "lepra cells" which are uniformly distributed beneath the epidermis (see Fig. 97, p. 527).

Immunity.—There is an allergic response in leprosy. The early reaction to *lepromin* is probably allergic; but it is not clear whether the late *true* reaction is the same. Contrary to the popular belief, there seems little doubt that there is a natural immunity to infection which varies in degree in different individuals. Susceptibility to infection may depend upon general health, because it is certain that debility from any cause lowers resistance to leprosy. Varying individual resistance is also exemplified by the type of the disease. The tuberculoid type with few bacilli, indicates a comparatively high resistance, and the multibacillary lepromatous form a comparatively low resistance. In the former, Mitsuda's skin (lepromin) test is usually strongly positive; in the latter negative. The suggestion has been made that this test may be employed in non-leprosy subjects as an index to resistance to leprosy. Applying it to non-leprosy children of leper parents, Rotberg (1936) found that positives increased with increasing age, reaching the maximum of 50 per cent. at the age of ten. This is taken to indicate that resistance is low in young children, but increases with age, but there is no evidence, as in tuberculosis, that resistance may be ultimately broken down by massive or repeated infections, whilst slight infective doses tend to raise resistance. It must be remembered, however, that the lepromin reaction is a non-specific one, hence many healthy persons may show a positive reaction. Several observers have shown that in such persons the positive lepromin reaction goes together with a positive tubercular reaction. Love and McNalty (1958) conclude that exposure to tuberculosis renders people allergic to the leprosy bacillus. They show, however, that no correlation exists between

these two tests when carried out on leprosy patients, for they found that only 55 per cent. of the tuberculoid patients and 59 per cent. of the lepromatous gave positive *tuberculin* reactions. Another indication of resistance is the abortive case, when slight, though definite, lesions appear and disappear without apparent cause. About the inheritance of acquired immunity there is still little clear knowledge.

In Burma leprosy is of a much more severe type in native Burmese than in Indians living in that country. Some authorities have claimed that racial immunity is the result of prolonged and intimate contact with leprosy at some remote period of history and its disappearance as an endemic disease has been explained on this basis, but there is really little evidence to support this. It is more natural to explain the persistence of endemic leprosy in certain European countries, and its disappearance from others, on the basis of improved sanitation and hygiene than on racial immunity. Chaussinand (1948) has put forward the view that there is a relative cross-immunity between tuberculosis and leprosy. While acknowledging that tuberculosis is often a fatal complication of lepromatous (anergic) leprosy, he stresses the fact that it is a rare complication of tuberculoid (allergic) leprosy; also, from a study of the epidemiological curves of tuberculosis and of leprosy in various countries, he concludes that leprosy declines as genetic immunity to tuberculosis increases.

Localized immunity is observed in active lesions, especially those of the tuberculoid type. In the annular form of eruption the active inflammation spreads at the margins while the disease dies down at the centre, leaving only a slight discolouration, or perhaps a mild sensory impairment; or, again, a major tuberculoid lesion may flare up and die down again, leaving only a slight visible scar to indicate its former site.

Clinical features.—*Incubation period.*—This is undoubtedly very variable and may be very prolonged: as long as 6 to 8 years. In South Africa the average period in nodular cases is about 2 years though it would be fair to state that the general average is $3\frac{1}{2}$ years, the extremes lying between $5\frac{1}{2}$ months and 4 years. It may well be that very long incubation periods may represent long latent periods after infection and before outward visible signs become apparent. Early discoloured anæsthetic patches may be overlooked for years. Thus the Editor in London diagnosed as leprosy a case which had been regarded as seborrhoea of the face and ears. In this instance the incubation period—that is before the disease became evident—appeared to be as long as 31 years. On the other hand, short incubation periods have been recorded in infants born of leprosy parents, and Dreisbach (1954) has reported an incubation period of five months.

In children of sufferers from leprosy living with their parents in the Culion Island colony in the Philippines it was observed that the disease developed in 22 children within 4 months to 4 years from the time of their removal from the source of infection. Certainly in one case it took place during the first year of life. Muir (1948) has recorded a case in a three months' old child. There appears to be direct relationship between closeness of contact with the diseased and the early development of symptoms. The length of incubation is considerably affected by the general health and habits of the patient, as well as by the climate. The first signs of

leprosy may appear during the course of some other disease, such as dysentery, enteric fever, malaria or influenza.

As compared with tuberculosis, one of the chief characteristics of leprosy is the absence of toxicity; enormous numbers of bacilli may be present in the body with few signs. The local inflammatory reactions to lepra bacilli vary within wide limits. Thus, in one patient the disease is so localized that it affects one small skin area or the main nerve supply. There may be acute inflammatory swelling, local pain, trophic, sensory and other disturbances. Bacilli can be demonstrated with great difficulty. In contrast, a second case may show involvement almost of the whole body, so that a preparation taken from any part of the skin may reveal numerous bacilli, though the patient is not acutely ill and is able to be about and do his work. The nerves are not noticeably thickened, and superficially the skin appears normal. At any stage during invasion sudden exanthematous reactions may appear, accompanied by fever and general symptoms.

The *chronic onset* is so gradual and insidious that the disease has advanced to a considerable extent before any abnormality is evident. There may be tenderness, tingling or thickening of a nerve, an area of anaesthesia, perhaps with some change in the appearance of the skin, insensitiveness to burning, formication, tingling or numbness of extremities. Discoloured skin patches may be mistaken for eczema or ringworm; these may at first be small, gradually increasing in size.

In the *acute onset* there are occasionally multiple lesions with less diffused margins, which tend to spread rapidly and which contain very numerous bacilli. The first noticeable sign may be an evanescent rash. The onset may be determined by some other acute disease, such as malaria or typhoid, which lowers the resistance. It may also be the sequel to chronic infection, such as syphilis, ancylostomiasis or chronic disease of the gastro-intestinal tract. The period of life may also have some bearing, e.g. extra strain imposed on the body during puberty, parturition and menopause.

Classification of leprosy. *Clinical types.*—The somewhat complex classification adopted by the Cairo Congress in 1938 has been modified and simplified by that of Rio de Janeiro in 1946 on the basis of the actual degree of resistance of the tissues to the leprosy bacillus. It has since been modified by the Congress in Madrid (1953) and the following is more acceptable according to recent work. Low resistance produces the definite histological picture of the leproma which appears in all tissues. High resistance produces a different picture known as tuberculoid. The first is the result of absence of tissue reaction; the second that of effective reaction, but there is a pre-lepromatous and a pre-tuberculoid incubation period in which the reaction to the bacilli is slight. The affected tissues during this period show changes which do not indicate the type which may eventually evolve and this form is known as *indeterminate*. There is a fourth type, in which the cellular reaction is intermediate between lepromatous and tuberculoid, known as borderline (dimorphous).

When the Madrid classification was drawn up little was known of the borderline (dimorphous) type, but further study has resulted in the descrip-

tion of a macular stage (Khanolkar and Cochrane, 1956) and of a polyneuritic stage (Jopling, 1956). Therefore the following classification is suggested:

Tuberculoid Type.

1. Combined dermal and neural—macular.
—infiltrated.
 - (a) minor tuberculoid
 - (b) major tuberculoid
2. Pure neural
mono- or polyneuritic.

Lepromatous Type.

1. Combined dermal and neural—macular.
—infiltrated.
 - (a) discrete, sometimes nodular.
 - (b) diffuse, never nodular.
2. Pure neural—not proved.

Indeterminate Group.

1. Combined dermal, neural—macular only.
2. Pure neural—mono- or polyneuritic.

Borderline (dimorphous) Group.

1. Combined dermal and neural—macular.
—infiltrated.
2. Pure neural—mono- or polyneuritic.



Fig. 99.—Egyptian girl, aged 11, showing acute early lepromatous leprosy.
(Dr. H. K. Giffen.)

Lepromatous leprosy.—This is the type of disease seen in persons with a negligible resistance, and leprosy bacilli are widely disseminated throughout the skin, nerves and reticulo-endothelial system. In addition, there may be bacillary invasion of eyes, testes, bones, and mucous membranes of mouth, nose, pharynx, larynx and trachea; one of the earliest signs in children is swelling and tenderness of the tip of the nose, œdema and infiltration of the alar cartilages (Fig. 99).

Skin lesions are multiple, small, symmetrically distributed, and take the form of macules, infiltrations (plaques), papules and nodules, all of



Fig. 100.—Lepromatous leprosy in an Egyptian.

(Photo, Dr. H. K. Giffen.)

which may be present in the same patient at the same time once the disease has become well established. The pure diffuse type is an exception and will be described later. The earliest skin lesions are macules; these are level with the skin and therefore cannot be palpated. They are small, circular or elliptical, are erythematous in light skins with sometimes a coppery or purple hue, and in dark skins they are coppery with sometimes a faintly hypopigmented background. They have a smooth and shiny surface, their edges are indistinct and they are not anæsthetic or anhidrotic. Owing to the fact that these macules are often difficult to see and are not associated with itching or anæsthesia, they may be ignored by the patient. They may be situated on any part of the body, but are unusual in the axillæ, groins, perineum, on the external genitalia or on the scalp. They are most commonly found on the face, buttocks and extremities, and on the limbs the flexor surfaces may be involved as well as the extensor, and the palms and soles as well as the backs of hands and feet.

Infiltrated lesions are raised above the level of the skin and give a

sensation of thickening when gripped between finger and thumb. Their distribution and colouring is the same as that of lepromatous macules excepting that they do not appear on palms and soles owing to the thickness and tightness of the skin. They are raised in the centre and slope away peripherally to merge imperceptibly with the surrounding skin, have a smooth and shiny surface, and do not exhibit sensory loss, unless situated in a region of skin which is already anæsthetic as a result of peripheral nerve damage. Papules and nodules make their appearance as the disease advances, and particularly favour the face, ears and buttocks. Ears should



Fig. 101.—Nerve leprosy : *main-en-griffe*. (Dr. H. K. Giffen.)

always be carefully examined, for the lobes are more constantly affected than any other part and appear thickened quite early in the course of the disease, such thickening being readily confirmed by palpation with finger and thumb. Advanced infiltration and nodulation of the face give rise to leontiasis, or "leonine facies," in which the normal wrinkles on the forehead and cheeks have become deep furrows (Fig. 100). Nodules and infiltrations may undergo superficial necrosis and ulceration, and large ulcers may form on the lower legs when leprous infiltration of the skin is associated with chronic bilateral lymphœdema, secondary to massive bacillary invasion of the lymphatics. Thinning of the eyebrows is common, commencing in the lateral half and sometimes progressing to complete loss of eyebrows and eyelashes (superciliary and ciliary madarosis). Alopecia may occur, but is uncommon.

One particular variety of skin infiltration requires separate mention, namely, the pure diffuse type described by Lucio and Alvarado in Mexico in 1852 and later by Latapi in 1988. The skin of the whole body becomes

diffusely infiltrated (no macular stage being observed) rendering it stiff and smooth as in scleroderma. There is no obvious disfigurement apart from loss of eyebrows and eyelashes which always occurs, but there may be widespread small telangiectases, nasal destruction may develop, and sometimes there is alopecia and loss of body hair. Laryngeal ulceration has been recorded, but cutaneous nodules and ocular involvement are absent. Mexican physicians have described, in these patients, a unique form of lepra reaction known as "Lucio's phenomenon"; this will be described later under "Reactions."

Nerve involvement, in the absence of skin involvement, has not been described in lepromatous leprosy, but combined dermal and neural changes are a usual finding. Nerves do not show signs of damage as early as in the other types of leprosy, but nerve thickening and associated sensory or motor dysfunction can usually be demonstrated as the disease advances. As sensory loss is often more pronounced than muscular wasting, patients continue to use the affected limbs and the skin suffers much damage from repeated trauma owing to insensitivity to pain. Thus the hands become scarred from injuries and burns, and trophic ulcers develop on the soles of the feet. Nerve thickening, like skin involvement, tends to be bilateral and symmetrical, but there may be a difference in degree on the two sides. It is found in those peripheral nerves which are superficial in some part of their course, the thickening being localized to the superficial portion, e.g., the great auricular nerves in the neck, the supraclavicular nerves as they cross the clavicles, the ulnar nerves just above the elbows, the antebrachial cutaneous nerves in the forearms, the radial and median nerves at the wrists, the femoral cutaneous nerves, the common peroneals as they wind round the necks of the fibulæ, the superficial peroneals in front of the ankles and the posterior tibial nerves immediately below the internal malleoli. The earliest sensory disturbances may take the form of paræsthesiæ, hyperæsthesia and hyperalgesia, to be followed later by impairment of light touch, temperature or pain sensation. All three modalities should be tested when examining a patient, as sometimes only one is affected (dissociated anæsthesia); in such a case it is usually the ability to differentiate between hot and cold which is lost first. Loss of position sense, vibration sense and tendon reflexes may occur, but not commonly. Muscle wasting may produce deformities such as claw hand (ulnar nerve), "main en griffe" (combined ulnar and median nerves), dropped foot (common peroneal nerve) and facial palsy (facial nerve), but careful examination of muscles will show evidence of weakness long before paralysis occurs (Fig. 101).

Involvement of autonomic nerves manifests itself, in the early stages, by slight œdema of the hands or feet; more marked vaso-motor disturbance develops later causing the skin of hands and feet to be puffy and cyanosed.

In addition to skin and nerves the following tissues may be involved in lepromatous leprosy:—

Nails of fingers and toes.—These are affected when trophic changes take place in digits, and appear dry, lustreless, narrowed and longitudinally ridged.

Mucous membranes.—The patient may complain of nasal discharge,

possibly bloodstained, and of blocking of the airway, and examination reveals hyperæmia and swelling of the mucosa together with nodules or ulcers on the nasal septum. Ulceration leads to septal perforation and later to cartilage destruction and consequent "saddle-nose" deformity. Nodules may also form on the lips, tongue, palate and larynx, leading to ulceration. Laryngeal involvement gives rise to hoarse cough, husky voice and to stridor (leper voice). Oedema of the glottis, occurring as part of a reactional state, used to be a dreaded complication in the pre-cortisone era, calling for immediate treatment by tracheotomy. Perforation of the palate may occur in the absence of syphilis or yaws.

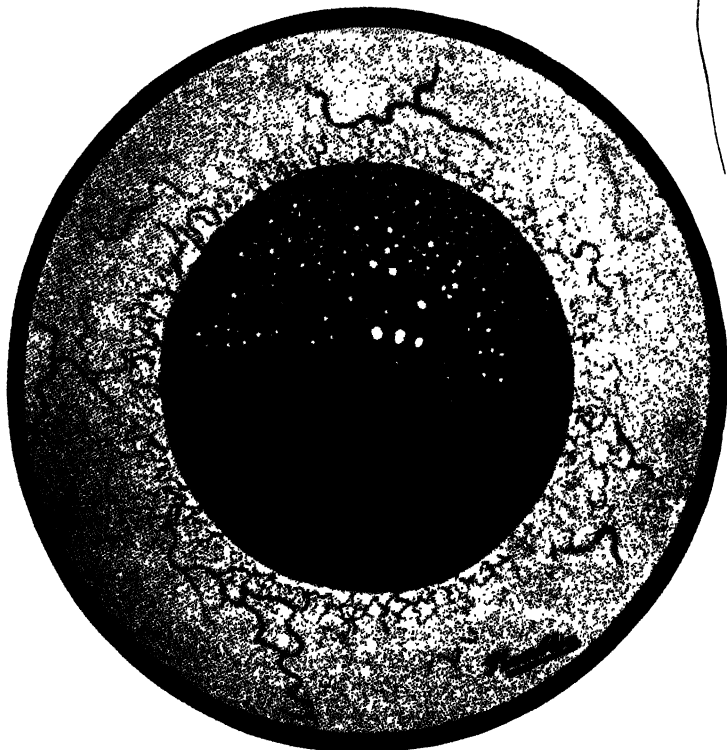


Fig. 102.—Leprosy of eye, showing characteristic pannus and superficial punctate keratitis. (Col. O'G. Kirwan.)

Eyes.—The structures of the eye which are commonly involved in lepromatous leprosy are the sclera, the cornea, the iris and ciliary body. Scleral involvement occurs early, and yellowish gelatinous nodules appear at the sclero-corneal junction where the anterior ciliary nerves penetrate. They are usually found on the temporal side, bilaterally, and may extend around the limbus to give rise to various types of keratitis as a result of extension into the cornea. Superficial punctate keratitis is the commonest type and is considered pathognomonic (Kirwan, 1955; Holmes,

1957). It is characterized by a milky haze over the upper portion of the cornea punctuated by tiny white spots resembling grains of chalk (Fig. 102). These spots are miliary lepromata. These changes can be seen quite well with a corneal loupe and a torch, but are best seen with the aid of a corneal microscope and slit lamp. By this means one may demonstrate glistening nodules along nerve filaments in the cornea. Pannus is very common and takes the form of a net, the meshes of which are composed of uniform branching blood vessels, in contradistinction to the pannus of trachoma in which the new blood vessels are terminal and arranged in bundles (Kirwan, 1955). A solitary leproma may develop on the cornea and may grow to a large size.

Miliary lepromata in the iris and ciliary body may lead to a slowly-developing chronic iridocyclitis of which the only symptom is steadily increasing bilateral blindness; or there may be a sudden onset of acute iridocyclitis, an allergic reaction to disintegrating leprosy bacilli affecting one eye or both eyes and characterized by pain, redness, photophobia and lachrimation. Lesions of the posterior segment have been reported.

The eyes may be affected by quite a different set of circumstances, namely as a result of damage to the trigeminal nerve or to the facial nerve.

Involvement of the fifth nerve leads to corneal anæsthesia and this in turn leads to corneal ulceration (neuropathic keratitis). Involvement of the seventh nerve causes facial palsy and may result in corneal ulceration consequent upon inability to approximate the eyelids (lagophthalmos). This is known as exposure keratitis.

Bones.—Changes in bones in lepromatous leprosy are confined to the skull and limbs. In the limbs the changes are almost solely concentrated in the hands and feet and are due to a combination of factors which include: (1) Deposition of bacilli; (2) neurotrophic atrophy; (3) repeated trauma resulting from analgesia; (4) Disuse owing to paralysis and contractures; (5) secondary infection from trophic ulceration; (6) generalized osteoporosis of hormonal origin. Deposition of bacilli in the medullary cavities, the periosteum and the nutrient vessels gives rise to bone cysts,



Fig. 103.—Late effects of nerve-leprosy of 22 years' duration. (Dr. H. K. Giffen.)

enlarged nutrient foramina, aseptic necrosis, and spindle-shaped leprous dactylitis closely simulating that of tuberculosis or syphilis. Leprous periostitis of the tibia, fibula and ulna have been described. Neurotrophic atrophy affecting the hands is localized to the phalanges, commencing with shortening and gradual disappearance of the distal phalanges, followed by gradual melting away of the middle and proximal phalanges in turn. Metacarpals and carpal bones are spared. In the feet the atrophic changes are localized to the metatarsals and phalanges, commencing in the proximal phalanges or in the heads of the metatarsals. In the proximal phalanges the diaphyses become gradually thinned by rarefying osteitis, known as

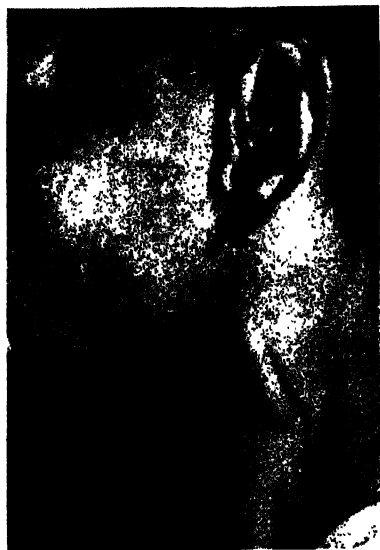


Fig. 104.—Gross thickening of great auricular nerve in tuberculoid leprosy. (*Sir George McRobert.*)

“concentric bone atrophy,” so that eventually there is but a fine needle of bone left. This may be followed by disappearance of the affected bones, and the shortened toes are connected to the foot by soft tissue only (see Fig. 108).

In the metatarsals absorption begins at the distal ends which become thinned and pointed—the “sucked candy stick” appearance. The tarsal bones are spared.

Sensory loss results in repeated trauma, both major and minor, and this is an important contributory factor to the production of bone atrophy and absorption. Brand (1954) states: “By far the greatest proportion of finger absorption is secondary to burns and trauma which follow anæsthesia.” In addition, sensory loss can lead to the development of Charcot joints in the fingers, toes, wrists or ankles.

Muscle paralysis can lead to disuse and, in neglected cases, to fibrous or bony ankylosis of the interphalangeal, metacarpophalangeal and metatarsophalangeal joints. Disuse also results in osteoporosis owing to decreased osteoblastic activity.

Secondary infection commonly follows neglected trophic ulceration of feet or hands and results in pyogenic osteomyelitis.

Generalized osteoporosis may follow defective production of testosterone as a result of testicular damage.

Changes in the skull in lepromatous leprosy consist of atrophy of the anterior nasal spine and the maxillary alveolar process, probably caused by a combination of aseptic necrosis—due to leprous endarteritis—and pyogenic osteomyelitis due to gross ulceration in the nose.

Reticulo-endothelial system.—Lymph glands may be enlarged and painless, with the consistency of soft rubber, particularly the femoral,

inguinal and epitrochlear glands, but occasionally one or more glands become very swollen and tender as part of a reactional state. The reticulo-endothelial elements of the abdominal viscera are invaded by bacilli, especially in the spleen and liver, and the red marrow is similarly invaded. Lymphoedema of the lower legs may occur, giving rise to elephantiasis in neglected cases.

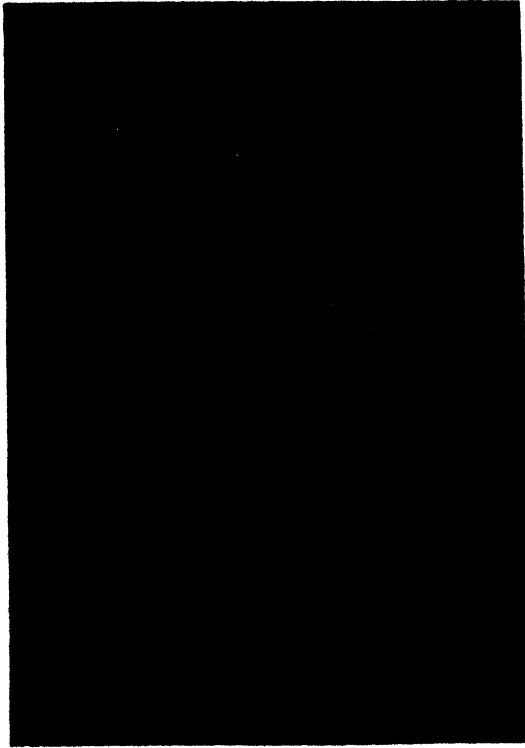


Fig. 105.—Tuberculoid leprosy in an Indian. This was a solitary lesion, anæsthetic, with raised red margin. The ulnar nerve was thickened.
(Sir George McRobert.)

Testes.—Testicular atrophy may occur, resulting in sterility and gynæcomastia.

Tuberculoid Leprosy.—This is the type of disease seen in persons with a good resistance and may be purely neural or combined neural and dermal. The infection is never widespread but is localized to one area or to a few areas asymmetrically. Affected nerves are thickened, sometimes irregularly, and there are associated sensory or motor changes depending on the type of nerve involved. Sensory disturbance occurs as described under lepromatous leprosy excepting for the fact that it occurs earlier in the course of the disease and can be noted before the onset of skin lesions. If

the patient complains of sensory disturbance such as paræsthesiæ or anæsthesia, a search must be made for palpable thickening of the nerve responsible for the sensation of that area, e.g., face—trigeminal nerve; neck—great auricular nerve; (Fig. 104) forearm—antebrachial cutaneous nerve; fifth finger—ulnar nerve; hand—median nerve at the wrist; thigh—femoral cutaneous nerve; lower leg—common peroneal nerve at the neck of the



Fig. 106.—Trophic ulcer in leprosy. (*Sir George McRobert.*)

fibula; dorsum of foot—superficial peroneal nerve; sole of foot—posterior tibial nerve just below the internal malleolus. Loss of position sense, vibration sense and tendon reflexes occur rarely. Motor changes are shown by muscle weakness or wasting and must be sought in the face, in the intrinsic muscles of the hand and in the dorsiflexors of the foot. It is extremely rare for the dorsiflexors of the wrist to be affected owing to the fact that the radial nerve in the arm and forearm follows a deep course among the muscles and therefore escapes leprosy involvement. It is interesting to note that the same nerve, when it becomes superficial at the

end of its course, often becomes thickened and can be palpated as a firm mobile cord as it lies against the lower end of the radius.

Skin lesions take the form of macules or infiltrations (plaques) (Fig. 105). A tuberculoid macule is erythematous on fair skins and hypopigmented (not depigmented) on dark ones, has a dry and rather rough surface, its edges are well-defined, and it is anæsthetic (except on the face) and anhidrotic. Infiltrated lesions are erythematous, whether on fair or dark skins, with sometimes a coppery, brownish or purple hue, have a dry and rather rough surface which may be irregular or pebbled, are sometimes scaly, have well-marked sensory loss and have edges which are raised



Fig. 107.—Dimorphous (Borderline) leprosy, showing early lepomatous changes.
(Sir George McRobert.)

and clear-cut while the centres show variable flattening. In dark skins the colouring of the lesions obscures the underlying hypopigmentation. Central healing and peripheral extension give rise to annular lesions in which the *outer* edges are raised and well-defined and the *inner* ones are flattened and indistinct. For descriptive purposes these infiltrated lesions are divided into minor and major tuberculoids (leprides), the major ones being larger, more grossly infiltrated and more deeply coloured.

Lesions of tuberculoid leprosy are usually few, large, asymmetrically situated, and favour the face, extensor surfaces of limbs, the back and buttocks, while tending to avoid the chest, abdomen, scalp, and the flexor aspects of limbs. If palms or soles are involved the lesions are not raised owing to the thickness and tightness of the skin. Sometimes one or two small "satellite" lesions are seen in the vicinity of a large plaque

and may look like nodules, but the fact that they are less elevated in the centre than at the edges can be confirmed by palpation. Thickened cutaneous nerves may be palpated in the vicinity of the lesions, but tissues other than skin and nerves are not involved directly. The eye may suffer indirectly from corneal ulceration when there is damage to the facial nerve (exposure keratitis) and also when there is damage to the trigeminal nerve (neuropathic keratitis). Loss of eyebrows does not occur unless there is an infiltrated lesion traversing the eyebrow, and then the loss of hair is confined to that portion of the eyebrow which is actually covered by the lesion.

Bone changes in hands or feet are less common than in the lepromatous type as leprosy bacilli are not deposited in the bones or their nutrient arteries; also, the early development of muscle wasting and paralysis results in disuse and therefore reduced risk of repeated trauma. However, neuropathic atrophy may occur in the phalanges of fingers or in the metatarsals and phalanges of feet, but, unlike the changes in lepromatous leprosy, they are never bilateral and symmetrical. Bone changes secondary to disuse, to loss of sensation and to trophic ulceration, may occur as described under lepromatous leprosy. Indolent ulcers of the feet are common (Fig. 106).

Borderline (dimorphous) leprosy.—This is the type of disease seen in persons with a limited or variable resistance, and usually presents with skin and nerve involvement. At the Sixth International Congress of Leprosy (Madrid, 1953) the existence of a pure neural form was not accepted, but careful observation since then has proved that a polyneuritic form does exist.

The infection is neither as strictly localized as in tuberculoid leprosy nor as widespread as in the lepromatous type, but is somewhere between the two. Some patients remain dimorphous throughout, but others progress to one or other of the two polar types depending on immunological factors not yet understood (Fig. 107).

Skin lesions are macular, infiltrated, or both, the earliest lesions being macules which are erythematous in fair skins, or hypopigmented (with sometimes an erythematous periphery) in dark skins. They may appear on trunk or limbs but have a predilection for the back, and in number and character are intermediate between the macules of the two polar types. Careful testing will reveal impairment of sensation in some if not all of the macules.

Infiltrated lesions have their own distinctive features in which the characteristics of the two polar types are merged. They are moderate in number, asymmetrical in distribution, their erythema has an admixture of purple or brown, their surface is smooth and often shiny, and they slope away peripherally from raised centres. The edges are well-defined in places and indefinite in others. Some of these infiltrations may take the form of bands, annular lesions and small nodules. Annular lesions have a characteristic form in which an oval area of normal-looking, but anæsthetic skin, is surrounded by a band of infiltrated tissue of varying width, the inner edge being raised and clear-cut (giving the oval area a punched-out appearance), the outer edge merging imperceptibly with the surrounding

skin. These should not be mistaken for annular tuberculoid lesions for in the latter the outside edges are raised and clear-cut while the inner edges are indistinct. Sometimes there is an oval band of infiltrated tissue, even in width and more raised in the central part of the band, which has well-defined outer and inner edges. Infiltrated lesions are invariably anæsthetic and may be found on any part of the body, with the exception of axillæ, groins, perineum and scalp, but favour the limbs and buttocks.

Nerve involvement can always be demonstrated in dimorphous leprosy, and often neurological symptoms such as paræsthesiæ and hyperalgesia precede the onset of skin manifestations. Nerves are involved asymmetrically and show palpable thickening and impaired function (sensory, motor, or both). Other tissues are not affected directly but only indirectly as in the tuberculoid type.

Indeterminate leprosy.—This is an early phase in the natural history of leprosy occurring in a proportion of patients. At this stage the disease has not yet determined into which type it is going to evolve. Manifestations may be neural or macular (or both), macules being nondescript with uncharacteristic histology and absence of bacilli. This group is likely to become increasingly unimportant once histological changes in skin and nerves receive more study and attention.

REACTIONS (REACTIONAL STATES)

This is a subject which is little understood and about which there is much disagreement among leprologists. Some use the term "lepra reaction" to cover all types of reaction, others confine the term to one particular type of reaction known as *erythema nodosum leprosum* which occurs solely in lepromatous leprosy or in dimorphous leprosy which is passing into the lepromatous type. Again, others are opposed to the term *erythema nodosum leprosum* and have put forward alternative names.

Basically there are two types of reaction. Firstly, there is an acute exacerbation or activation of the underlying disease which may occur in any type of leprosy, and, secondly, there is an allergic phenomenon which is confined to the lepromatous type.

Acute reaction (Acute Exacerbation; Acute Activation).—It is not known what change takes place in the host-parasite relationship to initiate a sudden exacerbation of the disease process, but this is a well-known complication in all types of leprosy which is liable to occur in the early stages of treatment, particularly if the dosage of the anti-leprosy drug is increased rapidly, or when the course of the disease is disturbed by pregnancy or intercurrent disease. All existing lesions become rapidly more swollen and erythematous, new lesions may appear, the numbers of bacilli in the lesions increase and neural symptoms become aggravated. In lepromatous leprosy nodules may ulcerate, new lesions often take the form of papules, and bacillæmia may occur. The patient remains afebrile. In tuberculoid leprosy the swollen lesions resemble erysipelas, but fever is not present and there may be swelling and pain in one or more of the affected nerves. Caseation sometimes occurs in such nerves with discharge of caseous material through the skin. Bacilli may be found in small numbers in the

lesions even though absent previously, and they disappear as the reaction subsides. Scaling of the lesions takes place during the subsiding stage. In borderline (dimorphous) leprosy the lesions assume an erysipeloid appearance, as in the tuberculoid type, followed by desquamation. Nerve pain and swelling may be associated, but caseation does not occur. There may be fever, œdema of hands and feet, and hyperalgesia of palms and soles. Nerve involvement may have serious sequelæ, as in the tuberculoid type, in the form of rapidly-developing claw hand or dropped foot.

Erythema Nodosum Leprosum.—This is an allergic type of reaction which is confined to lepromatous leprosy, or to dimorphous leprosy which is passing into the lepromatous type, and is not an exacerbation of the underlying disease. It appears to be more common in fair-skinned races. It does not appear early in the course of the disease, nor in the early stages of treatment, and appears to be associated with a change in the morphology of the leprosy bacilli to the granular stage. It can be precipitated by intercurrent infection, vaccination against smallpox, overwork and worry, the taking of certain drugs such as iodides and sulphonamides, and, particularly, by effective anti-leprosy drugs such as sulphones. The reaction is characterized by the appearance of crops of brightly erythematous nodules and raised patches varying in size from a few millimetres to 4–5 centimetres in diameter; these may be few or multiple, can occur on any part of the body apart from the scalp, palms and soles, and often appear on areas of skin free from leprosy lesions. They appear suddenly, usually in the evenings, the smaller ones disappearing by the following morning and the larger ones taking days or weeks to disappear, leaving a blue stain in the skin. The patient often complains of burning discomfort in the erythema nodosum lesions, and pressure on them with the finger may be painful. Their bright red colour disappears immediately slight pressure is exerted on them, but it returns as soon as the pressure is released. When numerous they are accompanied by constitutional symptoms which include intermittent fever, severe nerve pains, arthralgia, bone pains, acute iridocyclitis, orchitis, rhinitis, epistaxis, lymphadenitis, insomnia and mental depression. It should be noted that acute iridocyclitis and orchitis can be unilateral or bilateral. The fever has its fastigium in the evening and may be accompanied by rigors and drenching perspiration. In some cases the erythematous nodes develop central necrosis and ulceration, leaving atrophic scars.

The fundamental histological changes are in the smaller subcutaneous vessels and their branches in the dermis which show endothelial proliferation and perivascular cellular infiltration and œdema. Bacilli are present in these lesions but are not as plentiful as in ordinary leprosy nodules. Blood examination reveals a polymorpho nuclear leucocytosis, increased gamma globulin and a raised erythrocyte sedimentation rate.

A peculiar type of reaction has been reported from Mexico in patients suffering from pure diffuse lepromatous leprosy after the disease has been present for three or four years, called "Lucio's phenomenon" or erythema necroticans (Latapi, 1938). Erythematous patches appear, become purpuric, necrose in the centre and develop a black eschar which falls off in a few days leaving a superficial atrophic scar. This type of reaction

is probably a sub-variety of *erythema nodosum leprosum* as the histology is essentially the same.

Leprosy of nose and larynx.—Examination of the nose and septum reveals granulomatous lesions containing leprosy bacilli. In advanced lepromatous cases large perforating ulcers of the septum are often revealed. MacCormick (1957) states that in Puerto Rico the extensive active lesions of the larynx formerly encountered are no longer seen.

The involvement of the epiglottis of the arytenoid-epiglottic folds (vocal cords) and the ventricular bands, accounts for the harsh whispered "leper voice" and the harsh "leper cough."

Atrophic laryngeal strictures are seen in old "burned out" cases.

The most frequent lesions are lepromata of the epiglottis with subsequent destruction, scarring and thickening.

Diagnosis.—Early diagnosis is of the utmost importance, but many factors militate against it. It is, of course, easy to diagnose obvious and advanced cases. The ignorance of the patient, his dread of the disease, and the fear and superstitions of the general public may hinder prompt recognition. The earlier indications are the discoloured patches on the skin, and symptoms referable to involvement of the peripheral nerves, such as tingling or numbness, formication, or a feeling of woodenness in the limbs. Of fundamental importance are impairment of sensation, thickening and tenderness of nerves and demonstration of acid-fast bacilli.

To test sensation, the patient should be stripped and blindfolded. For testing anaesthesia to light touch, a feather should be used; analgesia is tested by pin-prick, using an area of normal skin as control. The two-pin test is often positive when the feather test is negative. Loss of thermal sensation is important and can be elicited by using a test-tube containing hot water and another containing iced water. Hyperaesthesia and paraesthesia may precede anaesthesia to light touch.

Thickened nerves may be felt on palpation, and tenderness elicited by striking an area sharply with the finger or patellar hammer. The ulnar nerve is commonly affected above the elbow: the common peroneal at the head of the fibula behind the knee; the superficial peroneal in front of the ankle; the terminal branch of the radial as it passes over the lower end of the radius; the posterior tibial below the inner malleolus; the great auricular as it runs parallel to the external jugular vein; and the branches of any particular nerve supplying a tuberculoid lesion.

Bacteriological examination.—This is essential in order to establish proof of the disease and to assist in correct classification and consists in carrying out a series of smears from the lesions. The scrape-incision method is recommended and is carried out as follows: The lesion is cleaned with ether and a fold is firmly held between thumb and forefinger of the left hand (to render it avascular); with a small-bladed scalpel an incision is made about 5 mm. long and 3 mm. deep, pressure of the fingers being maintained; the blade is then turned at right angles to the cut and the wound is scraped several times so that tissue fluid and pulp collect on one side of the blade; this is *gently* smeared on a glass slide. Smears are fixed

by heat and are then stained by Ziehl-Neelsen technique. By this method acid-fast bacilli will always be found in lepromatous leprosy and frequently in the borderline (dimorphous) form, but will usually be absent in the tuberculoid type (except in reaction) and in the indeterminate group. Nasal scrapings have been advocated in the past, but experience has shown that skin smears are far more valuable in diagnosis; not only are bacilli always readily demonstrated in the skin when they are present in the nasal mucosa, but often they are present in the skin when absent from the nose. For example, in borderline (dimorphous) leprosy, nasal scrapings may be negative when the skin smears contain large numbers of bacilli

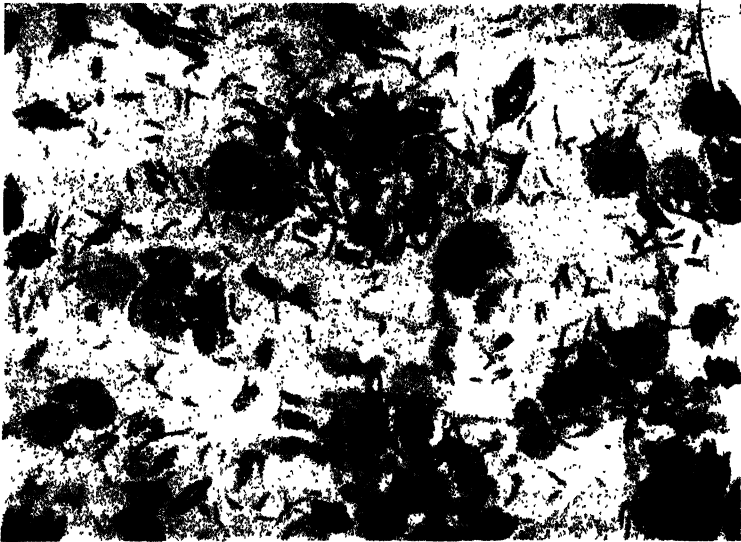


Fig. 108.—Biopsy of Acute Leprosy in the "lepra reaction." (The leprosy bacilli appear as dark rods.) (After Roland Chaussinand, Institut Pasteur.)

and it has been shown by Byers and Wolcott (1954) that bacilli may disappear from the nasal mucosa long before they disappear from the skin.

Biopsy of the skin is essential for correct classification as it enables the histological changes in the skin to be studied. In addition serial biopsies carried out at regular intervals provide a valuable method of assessing prognosis and treatment (Ridley, 1957) (Fig. 108). In carrying out a biopsy the most active part of the lesion must be chosen; this will be at the edge of the lesion in tuberculoid leprosy and in the centre in the lepromatous type. After ensuring local anaesthesia with two per cent. procaine a portion of skin is removed with a scalpel or by a skin biopsy punch possessing a circular cutting edge, 5–7 mm. in diameter. It is essential that the incision should reach the subcutaneous fat, otherwise the deeper layers of the dermis may not be included in the biopsy material. Paraffin sections are stained with hæmatoxylin and eosin to show the histological changes,

and with a modification of the Ziehl-Neelsen, using pinene (Lowy and Ridley, 1954) to demonstrate acid-fast bacilli. A nerve biopsy will be necessary in a purely neural case or where a skin biopsy has not given sufficient information, and for this purpose a thickened sensory nerve is chosen, such as the great auricular in the neck, the antebrachial cutaneous in the forearm, the radial at the lateral aspect of the wrist, the femoral cutaneous in the thigh, or the superficial peroneal on the dorsum of the foot.

In lepromatous leprosy bacilli can often be found in the sternal marrow, but this is not a practical method of diagnosis as bacilli are always readily demonstrable in the skin if present in the marrow.

Certain serum reactions which may be of assistance in diagnosis have been described under *Pathology*.

The lepromin reaction.—In 1919 K. Mitsuda, in Japan, introduced an intradermal test to assist in differentiating between the two types of leprosy, and the test has since borne his name.

Mitsuda originally used a boiled and phenolized suspension of ground-up lepromatous tissue in saline, but various modifications have been suggested since then in order to obtain, as far as possible, a suspension of heat-killed leprosy bacilli in normal saline. The method of preparation approved by W.H.O. Expert Committee on Leprosy (1953) is as follows: Nodular tissue from several lepromatous patients is removed under strict asepsis and extraneous tissue, such as fat and epidermis is trimmed. After autoclaving, the tissue is ground in a mortar with gradual addition of saline up to 20 ml. per grm. of tissue; then filtered through nylon. 0.5 per cent phenol is added to a filtered suspension which is then distributed in containers which are sealed and reheated. It must be emphasized that the *lepromin* is not a diagnostic test, for persons who have never been in contact with leprosy may have a positive lepromin reaction, if they are Mantoux positive; but taken in conjunction with clinical, bacteriological and histological investigations, it can play an important part in confirming the diagnosis and classification.

In lepromatous leprosy the *lepromin* reaction is always negative and in the tuberculoid type always positive. In the indeterminate group the reaction is variable; and in the borderline (dimorphous) it is usually negative, but sometimes weakly positive.

0.1 ml. is injected intradermally and the result is recorded as follows:

Early (Fernandez) reaction. Read at 48 hours.—Negative (—): absence of reaction, or erythema without infiltration, or erythema, without infiltration, not larger than 5 mm. in diameter.

Doubtful (+): erythematous reaction with an area of infiltration larger than 5 mm., but less than 10 mm. in diameter.

One-plus positive (+): erythema and infiltration 10–15 mm. in diameter.

Two-plus positive (++) : a similar reaction 15–20 mm. in diameter.

Three-plus positive (+++) : a similar reaction more than 20 mm. in diameter.

Later (Mitsuda) reaction. Read at 2–5 weeks.—One-plus positive (+): a nodule 4–7 mm. in diameter without ulceration.

Two-plus positive (++) : a nodule 7–10 mm. in diameter without ulceration.

Three-plus positive (+++) or an ulcerating nodule of any size.

The histamine test of Rodríguez and Plantilla (1931).—Differentiating leprosy from syringomyelia. A drop of 1 : 1,000 solution of histamine diphosphate is placed on the analgesic area and another drop on a normal area. A superficial pinprick is then made through each drop and this is followed by development of a weal at each puncture site. At the same time a red flare will form round the weal in the normal skin, but not in the analgesic area, and this is a sign that the intracutaneous nerves have been destroyed. In syringomyelia, where sensory loss is due to cord damage, both weals will be surrounded by a red flare.

The histamine test is described by Casals. By puncturing the skin with finger nails the formation of histamine by the tissues is produced. Where the cutaneous nerves are affected the erythematous reaction does not appear in early leprosy lesions, but shows up as a white patch on an erythematous background.

Subsidiary signs.—Anidrosis, often preceded by hyperidrosis, is characteristic of chronic cases, and is usually present in tuberculoid macules. In doubtful cases pilocarpine, 0.2 ml. of 1 in 1,000 solution, is injected intradermally in a suspected patch and a similar amount in adjacent healthy skin. Both areas are then painted with tincture of iodine and, when dry, powdered with starch. The control area sweats, turning the starch blue. Absence of sweat at the point of injection indicates leprosy.

A useful diagnostic aid is described by Arnold as the intradermal mecholyl test for anhidrosis. The action of mecholyl chloride (almost identical with acetylcholine) is similar to that of pilocarpine. Denervation of sweat glands by leprosy neuritis is the cause of anhidrosis, usually affecting the most distal portions of the post-ganglionic nerve fibres. In carrying out the test, equal areas of leprosy and healthy skin are painted with a solution of castor oil, iodine and absolute alcohol. Then 0.05–0.1 ml. aqueous solution of mecholyl chloride are injected intradermally at the border of the lesion so as to produce a weal. The whole area is lightly dusted with powdered starch as an atomizer. Within a few minutes sweat droplets appear on the functionally intact skin, which becomes blue from the iodine and starch combination. The response is negative when no sweat drops appear within the area tested.

The histamine test of Rodríguez is somewhat similar in slight or early cases. A drop of 1 in 1,000 solution of histamine is placed within the margin of the suspected area, and a second outside. A prick is made with a needle through the drop. A red flare appears in normal skin. This test can be of great value in a purely neural case with sensory loss in one or more limbs, for it will exclude hysteria and organic disease of the central nervous system, such as syringomyelia. In all those conditions a red flare develops in the anæsthetic skin, but no flare appears if the anæsthesia is due to leprosy or other forms of peripheral neuritis.

Differential diagnosis.—The characteristic marks of leprosy are sufficiently distinctive, but they have to be differentiated from psoriasis,

seborrhoeic dermatitis, various forms of tinea, eczema, lichen rubber planus, pellagra and filarial disease. Blastomycosis produces skin lesions reminiscent of leprosy. From syphilis and yaws, however, it may not always be so easy. Syphilitic and yaws skin lesions may often closely resemble the maculae of leprosy, but the absence of sensory changes and reaction to treatment are sufficiently distinctive. The Wassermann reaction alone cannot always be depended upon in differential diagnosis as syphilis and leprosy may co-exist; also a false positive reaction is not uncommon in lepromatous leprosy (see Pathology). *Leprophilia* is the name given for a hysterical condition with false anaesthesia developed by a peculiar kind of psychoneurotic who craves for sympathy.

The thickened skin of crab yaws on the feet may roughly resemble leprotic hyperkeratosis and may give a semblance of anaesthesia. Gangosa of yaws may be mistaken for nasal leprosy.

The early lesions of *mycosis fungoides* might possibly be mistaken for early nodular leprosy, and *leucoderma* is not infrequently associated with leprosy in the popular mind. It is extremely common, especially in India, and in negro races, and unfortunate sufferers are sometimes to be found in leprosaria (or leprosy institutions). Depigmentation in leucoderma, however, is more complete and sensory changes are absent. *Lupus vulgaris* and other tuberculides are very likely to be mistaken for leprides, and in both diseases acid-fast bacilli are difficult to demonstrate. *Lupus* evinces a greater tendency to scar formation and there are no sensory changes.

Cutaneous leishmaniasis and, in South America, *espundia*, may be mistaken for leprosy. The lesions on the skin of the face tend to concentrate round the mouth and nose and form a more raised margin than those in leprosy. Demonstration of the Leishman-Donovan body will always settle the matter, but leishmanial lupus-like lesions on the ears may cause difficulty (see p. 168). *Acrodynia*, burns and other injuries may leave behind anaesthetic scars. *Eunuchism* has been mistaken for leprosy on account of the absence of eyebrows and the smooth, shiny appearance of the skin.

Polyneuritic leprosy affecting the hands has to be differentiated from *syringomyelia*, in which analgesia and loss of heat sense are accompanied by retention of sense of touch and normal sweat function. The absence of nerve swelling and tenderness is important. The nerve injuries, caused by trauma of the ulnar nerve or by *cervical rib*, may possibly be called into question, but can be settled by X-ray examination. Bernhardt's syndrome, or neuritis of the lateral femoral nerve, may cause anaesthesia of the anterolateral region of the thigh. *Raynaud's disease* has been confused because of trophic changes, sometimes known as *neuralgia paræsthetica*, in which the nerve thickening is absent; *hypertrophic interstitial neuritis* (Dejerine-Sottas's disease) may cause confusion; this is a rare condition with thickening of nerves which may be so great as to render them conspicuous, and is accompanied by sensory and trophic changes, as in neural leprosy, and ultimate production of claw hand. *Von Recklinghausen's disease* (neurofibromata) may sometimes resemble leprosy. Scarring and anaesthesia caused by extensive herpes zoster on the chest may give rise to difficulty. Scleroderma, localized or diffuse, may be compared with lepromatous leprosy, but madarosis is not present, nerves are not thickened, acid-fast

bacilli are absent from smear and skin biopsy is diagnostic. The absence of fever and the presence of neural signs should differentiate tuberculoid leprosy in reaction from erysipelas. Erythema nodosum leprosum may be mistaken for other forms of erythema nodosum or for the Weber-Christian syndrome (a relapsing, febrile, non-suppurative, nodular panniculitis (*Brit. J. Dermat.*, 1925, 37, 301)).

Prognosis.—Leprosy may sometimes be a slight passing ailment, or may become the most repulsive loathsome disease known to man. The two important factors are concentration and distribution of bacilli in the body and resistance. Prognosis is more favourable in the tuberculoid than in the lepromatous type and prognosis in the indeterminate dimorphous groups is intermediate between these two. The maintenance of a high standard of general health constitutes a most important element in prognosis. Some patients, even with advanced nodular lesions, are known to have partially recovered. On the whole, the earlier a patient comes under treatment the more favourable the prognosis. Very spectacular changes are most often seen in patients with tuberculoid lesions.

The danger of contact.—The factors which predispose to the danger of contact are closeness and duration, the infectivity of the case, combined with the age and general health of the person exposed to contagion. A child may acquire the disease after even slight contact.

Causes of death.—Leprosy differs from tuberculosis in its low mortality. As a rule the victims do not die of leprosy so much as from intercurrent disease. They die from complications or as the result of crippling deformities. Death may be due to asphyxia from obstruction of the larynx or trachea, or to prolonged lepra fever. The two commonest causes of death in lepromatous leprosy are pulmonary tuberculosis and secondary amyloidosis.

TREATMENT

Sulphone treatment of leprosy.—A new era in treatment was ushered in by the report of Faget and his co-workers in the U.S.A. in 1949 on the good effect of Promin, and extensive use of sulphone compounds since then, in many parts of the world, has established that they constituted a definite advance. It is generally agreed, however, that a further step forward in the drug therapy of leprosy was necessary, for not only are sulphones slow in action but they may sometimes cause unpleasant toxic effects. Tuberculoid leprosy responds best of all, and resolution should occur within one or two years; treatment should then be continued for one year after this. In the lepromatous type one should speak of arrest rather than cure, and it may take 3–15 years to rid the skin of bacilli; sulphones should then be continued at half the maximal dosage for life. Dimorphous leprosy occupies an intermediate position, and sulphones should be continued, as for lepromatous leprosy, if the lepromin test is negative.

Probably the most widely used sulphone at the present time is dapsone (DDS; DADPS) also known as the parent sulphone as it is the basic substance to which all the disubstituted sulphone compounds break down when taken by mouth, and it has the added advantage of being by far the cheapest.

Before describing the various sulphones in current use in the treatment of leprosy, it must be emphasized that there is no evidence that any one compound can be considered more effective than any other, but experience has shown that some patients tolerate one compound better than another. The principal toxic effects are anæmia, hepatitis, dermatitis and psychosis, but only the first of these is at all common. Cyanosis is occasionally observed, but has never been satisfactorily explained. Sulphone may produce, in addition, certain side-effects which are not true toxic effects as they occur only in leprosy and can be produced by a number of unrelated drugs. These are known as reactions or reactional states and have been described earlier in this chapter.

Oral sulphone compounds. *Dapsone* (4,4'-diaminodiphenyl sulphone).—This is put up by various manufacturing chemists in 100 mgm. tablets, and the commencing dose is 25 mgm. twice a week. At the end of 14 days the dosage is increased to 50 mgm. twice a week and then by similar fortnightly increments to 100 mgm. twice a week. The dose is then raised, provided there are no untoward effects, by 50 mgm. every fortnight up to 350 mgm. twice a week, and when this maximal level has been reached the dosage scheme can be changed to 100 mgm. daily if more convenient. 700 mgm. per week will prove suitable for most adult patients in the tropics, but should it be desired to correlate dosage with body weight, as in treating children, the maximum dosage may be calculated as 14 mgm./kgm./week or 2 mgm./kgm./day.

Diasone (disodium formaldehyde sulphonylate derivative of DDS).—This is manufactured by Abbott in 0.3 gm. sugar-coated, orange-coloured tablets, and is a disubstituted sulphone which liberates DDS on ingestion as a result of hydrolysis in the stomach. Francis and Spinks (1950) estimate that the potency of Diasone is 18 per cent. that of DDS, and on this basis two tablets of Diasone are roughly equivalent to 120 mgm. of DDS. A suitable dosage scheme is $\frac{1}{2}$ tablet daily increasing by $\frac{1}{4}$ tablet every fortnight up to a maximum of two tablets a day.

Sulphetrone (Solapsone, B.P.C.: tetrasodium 4:4-di-(3-phenyl-1:3-disulphopropylamino) diphenyl sulphone).—This disubstituted sulphone is a Burroughs Wellcome preparation which is put up in 0.5 gm. tablets, but is of little value given orally as it is very rapidly excreted in the urine, mostly unchanged. Given parenterally it has a definite place in the treatment of leprosy and will be described later.

Diaminodiphenyl sulphoxide (DDSO).—This is manufactured by I.C.I. in 100 mgm. tablets and in chemical structure it is very similar to dapsone. Davey and his colleagues (1957) have reported favourably on it in dosage similar to that of dapsone.

Oral sulphone compounds which are now little used in the treatment of leprosy include promizole, promacotin, sulphone cilag, and the French drug, *diatox argentique*.

Parenteral sulphone compounds. “*Avlosulfon*” Soluble (I.C.I.).—This is a 40 per cent w/w aqueous solution of a disubstituted sulphone which breaks down in the body to liberate half its weight of DDS, i.e., 1 ml. “*Avlosulfon*” Soluble = 200 mgm. DDS. This has overcome the

difficulty presented by the fact that DDS is insoluble in water, and is preferable to suspensions of DDS in oil as these tend to be painful and to cause abscesses. Intramuscular injections are painless, the dosage being 0.25 ml. (50 mgm. DDS) twice weekly, increasing by 0.25 ml. every fortnight and remaining on the maximal dose of 2-3 ml. twice weekly.

Sulphetrone (Solapsone, B.P.C.).—This is a disubstituted sulphone made by Burroughs Wellcome which is put up in a 50 per cent. aqueous solution for intramuscular or deep subcutaneous injection. It breaks down in the body into a monosubstituted compound, and not into DDS, and toxic effects appear to be less than with other sulphones in common use. It has the disadvantage, however, of causing discomfort at the injection sites. The commencing dose is 0.5 ml. (0.25 gm. sulphetrone) twice a week, increasing by 0.5 ml. every fortnight to a maximum dose of 3 ml. (1.5 gm. sulphetrone) twice a week and continuing at this level.

Promin (Glucosulfone Sodium).—This is the first sulphone ever to have been used in the treatment of leprosy and now has largely been superseded as it is administered by daily *intravenous* injections. It is still used quite considerably at the U.S. Public Health Hospital in Carville, and the usual dosage is 1 gm. in 2.5 ml. daily, increasing by stages to a maximum of 5.0 gm. in 12.5 ml. This dosage is then given daily for six days a week with a rest period of one week in every three.

TREATMENT WITH DIPHENYL THIOUREA COMPOUND (Ciba), S.U. 1906. (Formerly DPT).—*Thiambutosine*—has outstanding bacteriological activity against *M. tuberculosis* *in vitro* and *in vivo*. It has been on trial in leprosy for four years (T. F. Davey). It is given in tablets containing 0.5 gm. In adults the initial dose is 0.5 gm., increasing by 0.5 gm. every fortnight, up to a maximum dosage of 2 gm. (four tablets daily).

Few adults need more than 2 gm. daily in a single dose. Children tolerate it well in the same doses per kilo as suggested for adults (0.5-1.5 gm. daily) according to age on the basis of 25-40 mgm. per kmg.

The freedom from toxic side effects is remarkable; it causes no gastric or intestinal irritation, but promotes a sense of tranquillity and well-being. Although it has been blamed for skin eruptions in tuberculosis this has not been encountered in leprosy. Possibly, on account of its relationship to thiouracil, it has an anti-thyroid effect. Those who develop neuritis on DDS make satisfactory progress with S.U. 1906.

It is more efficacious in lepromatous cases. At the end of one year all cases have shown satisfactory progress and the degree of resolution, clinical and bacteriological, was greater than among controls on routine DDS. Twelve patients have completed three years and eight months of treatment and progress is maintained. *Erythema nodosum* has been seen in 3 out of 44 and was easily controlled by injection of stibophen. The drug is especially valuable for patients who are hypersensitive to sulphones and to thiosemicarbazone. No drug sensitivity has as yet developed.

DPT is of special value in those whose response to DDS is unsatisfactory. In the field of chemotherapy several compounds show promise. *Diamino diphenyl sulphoxide* DDSO, is closely related to the sulphone group—*Vadrine* (2-pyridyl-(4)-1,3,4-oxidiazolone-5), Jopling and Ridley, is another.

Streptohydrazid, a combination of isoniazid and streptomycin, Dreisberg and Cochrane, is a third. Cycloserine is an antibiotic recommended by Pardo Costello.

Davey is getting good results from inunction of ethyl mercaptan (*Etisul* or *Ditophal*) which is absorbed from the skin when rubbed into the thighs. It is too irritating when given by the mouth.

The Treatment of Lepra reaction.—If this reaction occurs during the course of treatment the injections must be stopped, but if there is some complicating disease (such as malaria) this must be specifically treated. During the lepra reaction the patient should be confined to bed and the bowels freely evacuated. Alkalies are advisable: 60 gr. of *sodium bicarbonate* may be given four times daily. Intravenous injection of potassium antimony tartrate, $\frac{1}{2}$ to $\frac{1}{4}$ gr. three times weekly, has proved an effective desensitizer. Calcium lactate and calcium gluconate in large doses act as adjuvants.

Other drugs of value in leprosy. *Thiosemicarbazone compounds.*—Thiacetazone or TB1 (p-aminobenzaldehyde thiosemicarbazone) (or amithiazone) provides a useful alternative to sulphone, the adult dose being 25 mg. daily by mouth, increasing by 25 mg. every fortnight up to 150 mg. daily. Treatment is continued at this level but should not be given for more than two years as the bacilli are likely to develop resistance by that time. Toxic effects are uncommon and include: anorexia, nausea, vomiting, malaise, headache, dizziness, albuminuria, skin rash, conjunctivitis, anaemia, agranulocytosis and liver damage.

Streptomycin and *dihydrostreptomycin* are effective in leprosy, but expense and toxic action on the auditory apparatus preclude their use on a large scale.

Isoniazid (isonicotinic acid hydrazide: INH) has proved disappointing alone and has not been found to enhance the effect of sulphone when used in combination.

PAS (sodium p-aminosalicylate) has a beneficial effect in leprosy, but its action is too slow to be of any real value.

Antigen Marianum, an antigen made from *Mycobacterium marianum* in France, has been tried, but the results are unconvincing.

The management of reactions.—When reactions occur the dosage of sulphone or other anti-leprosy drugs should be reduced, but should be stopped temporarily if there is nerve swelling and pain. Relief of nerve pain may be obtained by one or more intraneural injections of procaine and hyalase (1,500 international units of hyalase dissolved in 1–2 ml. of 2 per cent. procaine solution), but systemic treatment with cortisone or prednisone should be instituted without delay if the reaction is affecting a vital nerve such as the ulnar or common peroneal and there is threatened muscle paralysis. Jopling and Cochrane (1957) recommend commencing with a daily dose of 100 mgm. of cortisone, or 20 mgm. of prednisone, in divided doses, and reducing the dose as symptoms subside. Should muscle weakness progress in spite of steroid therapy, surgical treatment is indicated in the form of a nerve-stripping operation as described by Gramberg (1955). Steroid therapy also has an important part to play in acute iridocyclitis,

severe *erythema nodosum leprosum* and in exfoliative dermatitis due to sulphone sensitization. Acute iridocyclitis calls for frequent instillation of drops of 1 per cent. hydrocortisone acetate or cortisone acetate and keeping the pupil dilated with 1 per cent. atropine drops; systemic therapy with cortisone or prednisone is rarely required. In severe *erythema nodosum leprosum* Jopling and Cochrane continue steroid therapy for as long as required, without interrupting sulphone therapy, commencing with 100 mgm. of cortisone or with 20 mgm. of prednisone daily and reducing to the lowest effective level. They find that short 5-day courses are often satisfactory, the dosage of cortisone being 100 mgm.-75 mgm.-50 mgm.-25 mgm.-12.5 mgm. Prednisone is given in one-fifth the dosage of cortisone. Cortisone causes sodium retention and potassium depletion, and it is therefore necessary to give 3-5 grammes of potassium chloride by mouth daily and to restrict salt intake, but prednisone has the advantage of not causing electrolyte disturbance in the body.

Surgical treatment to eyes.—Lagophthalmos, resulting from facial palsy, calls for a lateral tarsorrhaphy in order to prevent exposure keratitis, occlusion of the pupil as a result of iris adhesions can be corrected by iridectomy, and chronic dacrocystitis is best treated by surgical removal of the lacrimal sac.

Surgical treatment to limbs.—Brand (1953) has reviewed the surgical methods of hand reconstruction and stresses the importance of Bunnell's sublimis transplantation operation for bringing paralysed fingers into use. Foot-drop is another form of paralysis which can be corrected by tendon transplantation.

Plastic surgery can play a very important part in rehabilitating the leprosy patient, and its chief contribution is in the reconstruction of the nose, the creation of eyebrows by transfer of hair bearing skin, the removal of excessive skin folds from the face, and the correction of gynæcomastia.

Physiotherapy.—The important role of physiotherapy has been outlined by Ruth Thomas (1954) and consists in keeping fingers mobile in spite of paralysis, thus preventing fixed claw hand deformity. If finger joints have already become fixed, their range of movement can be improved by daily wax baths, exercises and corrective splinting. Weakness of the dorsiflexing muscles of the foot can be improved by systematic exercises and by wearing a plaster splint at nights.

General management.—A thorough clinical examination is necessary at the outset of treatment in order to bring to light any associated disease, and investigations should include an X-ray of the chest, a blood count, and examination of the stool and urine. From the time of admission to hospital the patient must prepare for the time when he will be discharged, and this involves keeping active in body and mind in order to maintain and improve his capacity for earning a living. The patient must also learn how to protect his anæsthetic hands from injury and his anæsthetic feet from trophic ulceration. He must wear gloves for manual work or when handling cooking utensils, and must be fitted with specially constructed footwear which will not only protect his toes from injury, but will be designed to reduce pressure on the heads of the metatarsals. If trophic

ulceration has already occurred the ulcers can usually be healed by a period of local treatment and complete bed rest. An X-ray of the foot is necessary in order to assess the condition of the underlying bones, and metatarsectomy may be necessary at this stage if there is evidence of secondary osteomyelitis. Once the ulcers have healed, the patient must be supplied with footwear designed to reduce weight-bearing on the healed areas, and he must learn to adjust himself to a reduced amount of walking and standing. The use of a bicycle can be a great help in this respect. Cynthia Fisher (1955) has developed the method of treating trophic ulcers by plaster casts.

The prophylactic treatment of the dry and exposed cornea in lagophthalmos, in order to prevent ulceration, consists in the wearing of protective goggles by day and an eye shield at night. Holmes (1957) advocates the local instillation of 1 per cent. methyl cellulose as a tear substitute, instead of oily drops such as liquid paraffin, as it has antibacterial properties.

Intra-nasal ulceration leads to crusting and blockage which will require nasal toilet morning and evening. An alkaline nasal douche such as Collunarium Alkalinum, B.P.C. is useful, followed by the intra-nasal application of Ung. Hydrarg. Nit. Dil., B.P.

Clinical improvement in leprosy marches far ahead of the bacteriological. It may well be that the granular forms of the bacilli, which become evident during treatment, represent non-viable forms of *M. lepræ*. The bacilli under the microscope have the appearance of fragmentation, granulation and reduction to fine dust. Globi appear in the smears—some full of bacilli; others empty.

Physiotherapy and rehabilitation.—These avenues are comparatively new and important from the psychological angle. The main aim is to win the confidence and co-operation of these patients and to try to help them to help themselves. Ruth Thomas has found with oil massage, wax therapy, electrical stimulation, passive and active exercises, great improvement, especially in leprosy of the hands, can be achieved. It is important that if some rehabilitation programme can be carried out at the same time as physiotherapy, the patient should have a reasonable hope of becoming active and useful once more. Some occupation, such as simple carpentry, has proved to be within the power of most patients.

Prophylaxis.—If children could be prevented from coming into contact with infectious cases, then the number of adults who would later become victims would be so few that leprosy would decline. In planning preventive measures the incidence of child infection and of infectious lepromatous cases should be ascertained. If the former should reach 25 per cent. of the total and 20 per cent. of the latter, then intensive preventive measures must be undertaken.

The patients must be segregated in special areas near villages connected with a properly equipped centre. General hospitals should be prepared to treat leprosy in out-patient centres set apart for this purpose and special research units should be developed and special measures instituted for the care, segregation and observation of children with leprosy. Propaganda and carefully planned special training are essential. In addition, a leprosy

survey must be carried out and arrangements made for the regular examination of all immediate contacts of leprosy patients. Those receiving out-patient treatment should not be allowed to beg in the streets, to keep shops, or handle food. Early diagnosis and treatment play a very important part in the prevention of the spread of the disease. Hence the importance of effective methods of case-finding. The use of B.C.G. in the prophylaxis of leprosy is now being investigated in many parts of the world, but more time must elapse before its value is known. The basis for using B.C.G. is the theory that persons with an immunity to tuberculosis also harbour an immunity to leprosy. This is supported by the fact that persons with tuberculoid leprosy rarely develop pulmonary tuberculosis, whereas those with lepromatous leprosy often do. In view of the cases with which a negative lepromin reaction in non-leprous persons can be converted to a positive one by B.C.G. vaccination, large scale trials of B.C.G. vaccination in lepromin-negative children are now being carried out in order to discover if the incidence of leprosy in the vaccinated children is less than in those who have not been so vaccinated.

Even if the incidence of leprosy among the vaccinated groups is not reduced, it must be a significant advance if it could be shown that the incidence of tuberculoid cases was appreciably greater in the vaccinated groups.

CHAPTER XXXV

YAWS (FRAMBOESIA)

Synonyms.—Pian; Framboesia; Boubas (Brazil); Coko (Fiji); Parangi¹ (Ceylon); Dube (Gold Coast); Purru (Malaya); Tonga (New Caledonia); Dichuckwa (Bechuanaland).

Definition.—Yaws is a contagious inoculable disease, characterized by primary sore and indefinite incubation period, followed usually by fever, rheumatic-like pains, and the appearance of papules which generally develop into a fungating, encrusted, granulomatous eruption. Running a chronic course, it usually protects against a second attack. The disease is caused by *Spirochæta pertenuis*, and is controlled by penicillin. The organisms of yaws and syphilis are indistinguishable and the lesions produced are difficult to differentiate.

History.—Deductions from historical records suggest that yaws is of more ancient lineage than syphilis. It is clear that what we now know as syphilis appeared with dramatic suddenness at the end of the fifteenth century and, as a new and devastating disease, spread rapidly over Europe after the return of Columbus to Spain. Oviedo (1478–1557) was in Barcelona at the time, and in his *Historia General y Natural de las Indias*, he stated that it was contracted from Indian women by the Spaniards who accompanied Columbus; that it was brought by them to Spain, and transmitted to the army of Charles VIII. Las Casas (1474–1556), in his *Historia de las Indias*, refers to a disease which was very dangerous to Spaniards, and was called syphilis, being known in Italy as the “French malady.” Ruy de Isla, a physician practising in Barcelona in 1493, gives a very complete account and states that it was unknown before that year, and that it was brought by the crew of Columbus on their return from the *first voyage* to Haiti.

It is known that yaws often occurred in epidemic form on board slave ships and it may well be that the disease was an African importation into the New World. Much has been written of the possible identity in former times of such diseases as the “button sourvy” of Ireland, “sibbens” of Scotland and “rade-syge” of Norway and Sweden. It may well be that during the seventeenth and eighteenth centuries they represented a severe form of syphilis.

It may well be that yaws and syphilis have sprung from a common ancestor. In yaws it is probable that the spirochæte, under the more primitive conditions of the tropics, has spread from man to man by intimate contact, whilst the syphilitic spirochæte under more civilized conditions, where such contact is not possible, came to be communicated by the venereal route, thereby assuming a more virulent character and evolving (as do certain other spirochætes) neurotropic strains. Intermediate forms between the two classical forms of these diseases, which are so closely related as to be zoologically referable as “sub-species,” undoubtedly have become evolved in time, as in the non-venereal childhood syphilis of the Arab tribes of the Euphrates and Iraq, known as “Bejel” (Hudson). This disease (also known as Firzal, Latta, Laghoul, and Jirar) has been well described in Deir-ez-Zor in Syria, where there is a high

¹ This word means “foreigner,” a term applied by the natives to the European invaders of Ceylon.

incidence of syphilis, but very little gonorrhœa. This syphilis is spread by personal contact, is of low virulence, gives a positive Wassermann reaction, and corresponds to the endemic syphilis of Asia Minor, Syria, Iraq and Bosnia described by von Düring. The most frequent lesions are in the mucous membranes of the mouth; but in other respects—in the special affinity for children, and in the production of hyperkeratosis and depigmentation—it resembles yaws, and cirsinate lesions of the soles of the feet, resembling crab-yaws, are common. Depigmentation of the dorsum of the hands resembles that described by Lacapère in Morocco, but Hoff and Shaby state that meningo-vascular lesions may still be observed amongst these peoples. It is also found, as *Novojerz*, in S. Rhodesia.

Some consideration should be paid to the expressed views of Hudson (1946). In its extended sense he thinks that “*treponematosis*” is a widely distributed disease caused by one species, *Treponema pallidum*, that this disease presents different clinical patterns under different climatic and sociological conditions; that any variations in the parasite itself are functional representing strains which may, or may not, have fixed biological characters. On this basis he includes yaws, syphilis, bejel and pinta under one heading and would thereby discount the theory of the American origin of syphilis as objectionable and as just an historical fairy tale.

Geographical distribution.—Yaws is common in tropical Africa, West Indies, Ceylon, Pacific islands, Papua, the East Indies, and the Malay States. In India and China it appears to be rare. Children in the West Indies and Fiji are especially liable. During recent years it has become extremely prevalent in Kenya Colony, Tanganyika Territory, and Uganda, where it is spreading with great rapidity. On the other hand yaws has disappeared to a great extent from Guiana, Fiji, Ceylon and Barbados, where it was previously extremely rife.

Epidemiology and endemiology. *Contagion and heredity.*—As yaws is highly contagious, all circumstances favouring contact with the subjects of the disease favour it. Simple skin-contact does not suffice; a breach of surface is necessary. The knowledge that the secretions from yaws lesions could transfer the disease to another person was well known to the slaves of the West Indies, and they practised auto-inoculation in their children who did not show a generalized eruption.

The disease frequently commences in a pre-existing ulcer, the organism (spirochaete) being often conveyed by flies to the previously lacerated surface. Cases originate in certain dirty houses, the virus from previous yaws patients seemingly impregnating the floors and walls of the filthy huts. In this manner the disease may be, and in some cases no doubt is, acquired without direct transference from an existing case. In some countries, as in Ceylon, yaws is a disease of the flat, low-lying districts, while practically absent from the hill country; in Assam, on the other hand, it is more common among the hill tribes than among dwellers of the plain. Ramsay has shown in Assam that native hill people, who only exhibit obscure lesions, such as condylomata, while living at high altitudes, develop florid yaws when they come down to the plains. In Jamaica, Saunders and Kumm have emphasized the importance of rainfall and geological formations on the distribution of yaws. Wherever there is porous limestone there is little or no yaws.

Yaws is neither hereditary nor congenital. A pregnant mother suffering from yaws does not give birth to a child suffering from the disease, nor one which will subsequently develop yaws, unless the virus be first introduced directly through a

breach of surface after birth. It is not conveyed by the milk ; nor does a suckling suffering from yaws necessarily infect its nurse.

This statement should be qualified by the well-known fact that a syphilis-infected mother does not inevitably transmit the disease to her offspring, and if she does transmit, she may do so irregularly, not to one child, but to the next, and to one only of twins.

Although two-thirds of the cases in the West Indies, Pacific Islands and Ceylon occur before puberty, no age is exempt. In Jamaica the peak of the infection rate is about eight years. No new infections are found after thirty. Three males appear to be infected to every one female. It has been frequently remarked that yaws shows a predilection for certain native races. On the whole, the negro and negrito stock is specially liable to severe attack.

Yaws at the present day shows a striking limitation to the tropics, but it is a disease so readily communicable by direct contact that it seems remarkable that it does not spread in temperate regions. In the tropics yaws is limited to low level areas, and to rural districts with primitive sanitation. In Haiti, for instance, yaws is the disease of distant villages, and syphilis with chancre is common in the main town. In the Philippines the same is true : in the country, yaws ; in Manila, syphilis.

In Brazil yaws is still prevalent; in the Cameroons it occurs both in forest and in coastal areas. In the Sudan it is commoner in pastoral than in agrarian peoples: in Angola yaws occurs mainly in densely populated areas. In N. Rhodesia the disease known as *Novojera* is probably yaws. In Uganda the Nilotic peoples are chiefly affected. In Ceylon, Guadeloupe and Guam, yaws has disappeared. In Jamaica the incidence has fallen from 90 to 1 per cent. In the Marshall Islands it has fallen from 100 per cent. to almost nil. In the Fiji Islands much the same transformation has taken place. In the Philippines the fall has been from 10 to 2 per cent.

Ætiology.—In 1905 Castellani demonstrated in scrapings of yaws tissues an extremely delicate spirochæte—*Spirochæta pertenuis*, or *Treponema pertenuis*—very like that of syphilis. To demonstrate this spirochæte, slides should be prepared from scrapings of an incised yaw papule before it has ruptured. The films may then be stained with Giemsa, or made by the Indian-ink method; better still, the living parasites may be detected in fresh undried films by dark-ground illumination. A fully developed yaw is unsuitable, because it has been exposed to external sources of contamination and a variety of organisms will be present and may confuse the observer. Dobell and others have been unable to distinguish any structural differences between this spirochæte and *S. pallida* of syphilis (Fig. 5, p. 924). With the aid of the electron microscope the appearance of flagella and an undulating membrane can be made out. Sequiera (1956), who has studied the movements of pathogenic spirochætes which were described by Schaudinn and Hofmann as spiral, but which in *S. pallida* and *S. pertenuis* are really flat waves, but in *S. refringens* are really right-handed spirals.

S. pertenuis has been found in the spleen, lymphatic glands, and bonemarrow ; doubtless it also occurs in the blood. It is inoculable into monkeys and rabbits ; in the former, especially in the orang-outang, it gives rise to lesions similar to those in the human subject.

Cultivation of *S. pertenuis* was successfully performed by Noguchi in ascitic fluid containing a piece of fresh animal tissue, such as the kidney, the whole being covered with a layer of sterile paraffin. This rather complicated technique has been simplified by the later work of Hata, who substituted horse-serum, the inoculation being made through the upper solidified layer. Strict anaerobiosis is necessary but others have found it more difficult.

Turner and Hollander (1957), as the result of investigations carried out at the International Treponematoses Centre (Johns Hopkins), have shown that the diseases produced by these spirochaetes are not fundamentally different. The organisms isolated from the main forms of spirochaetoses (Treponematoses) produce similar experimental lesions. There is a linear relationship between the number of these organisms and the incubation period in the rabbit.

With an intradermal inoculum of 500 spirochaetes the incubation period is 17 days; with a ten-fold increase in their numbers, this period is shortened by about 4-5 days.

There is a correlation between the development of the clinical disease and the histological changes. The initial stages are characterized by the production of a mucoid material which is hyaluronic acid. In the second stage there is infiltration of mononuclear leucocytes. It is possible to divide the strains of spirochaetes

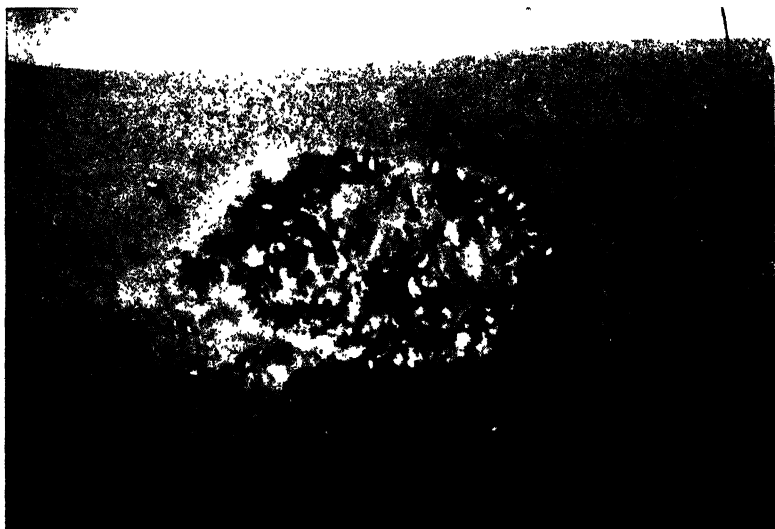


Fig. 109.—*Hippelates* flies on a yaws ulcer. Showing method of spread by these insects. (Dr. L. A. León, Quito.)

into three categories, according to the lesions observed in the rabbit and in the hamster. The first includes strains from patients with syphilis which cause indurated lesions at the site of inoculation.

The type from yaws causes only minimal changes at the site of inoculation. The third type includes strains from endemic syphilis groups and in rabbits it causes reactions intermediate between the first two. All these three types have common antigens. It appears that 35° C. is the temperature most favourable to the development of spirochaetes. At temperatures below 30° C. they multiply slowly, if at all. The influence of temperature is important and even decisive in the localization of spirochaetal lesions. Thus in the rabbit, whose internal body temperature is normally 39° C., lesions of the internal organs are rare. On the other hand ears, skin, testes and extremities, whose temperature is lower, constitute the preferential sites of either primary or metastatic lesions. In a rabbit, partially shaven, the lesions do not appear on the part protected by fur which

has a higher temperature. The action of *cortisone* is interesting as it causes a tremendous overgrowth of spirochætes in both initial and secondary foci.

Kumm has brought forward strong evidence that in Jamaica, at any rate, a minute fly, *Hippelates papillipes*, carries the spirochæte from one person to another (Fig. 109). He collected the flies at the rate of 5,000 per hour from one ulcer; they crawl under the scab and ingest large numbers of *S. pertenuis*, which are afterwards regurgitated. *H. papillipes* is an ocsinid fly having peculiar mouthparts, with projecting spines on the pseudotracheæ and labellæ (see p. 1079). *Musca spectandra* has been incriminated in Africa.

Inoculation into monkeys.—The most extensive and minute observations of Schöbl on *Cynomolgus philippinensis*, with emulsified extracts of yaws lesions containing *S. pertenuis*, deserve mention. The injections were made on the nose, eyebrows and scrotum. From three to five weeks after inoculation, papules appeared, corresponding to the typical yaw. Later, they spread peripherally like the ring-worm form of this disease. The disease in the monkey on first inoculation runs its course without developing into diffuse secondaries, but generalized yaws is produced by superinfection. Other late manifestations, such as lupus-like ulcerations and keratoderma of plantar surfaces, resemble those seen in man.

Human inoculation.—The fact that the disease could be transferred by secretion from yaws lesions was well known to the slaves in the West Indies. Charlouis and others have inoculated yaws patients with syphilitic virus and have produced a chancre at a site of inoculation. Schöbl considers that *S. pallida* is panblastotropic with a tendency to invade and multiply in all tissues and produce lesions, but is mesoblastotropic in its tendencies. Syphilitic lesions are found in the skin, mucous membranes, bones and muscles, viscera and nervous system. The spirochætes invade the cardio-vascular system and enter the placenta, giving rise to congenital syphilis. The yaws spirochæte is epiblastotropic, invading certain tissues, particularly the skin and bones; the nervous and cardio-vascular systems are not usually invaded and the disease is not congenital. It is suggested that in the few instances, in which lesions of the internal organs and cardio-vascular system have been reported, co-existing syphilis has not been rigidly excluded.

Yaws, moreover, shows a striking limitation to the tropics, and the effect of climate upon it is such that it does not spread in temperate climates from cases which are introduced.

Yaws spirochætes are unable to penetrate unbroken skin surfaces. Auto-inoculation may occur during the early course of the disease in man; the infection may spread to other parts of the skin, but mucous membranes are not invaded.

Other animal inoculations.—Nichols originally showed that yaws, like syphilitic lesions, can be produced in the testis of the rabbit, though the incubation period is shorter. Pearce and Brown observed, in intratesticular inoculation with *S. pertenuis* in the rabbit, a granular and finely nodular periorchitis, a lesion different from that of *S. pallida*. Turner and Chesney in Haiti found that, in rabbits injected with *S. pertenuis*, the testicular lesions consisted of miliary granules in the tunica and epididymis, but that general enlargement and induration (so common after inoculation with *S. pallida*) do not occur. Immunological differences between *S. pallida*, *S. pertenuis* and *S. cuniculi* have been found and in rabbits the spirochætes of bejel appear to be intermediate between those of syphilis and yaws.

Pathology.—A feature of yaws lesions is the great thickening of the epidermis and degeneration in the epithelial cells. In later stages there may be hyperkeratosis. The elongated papillæ are vascular, and are infiltrated with lymphocytes; leucocytes and plasma cells are also numerous. In contrast with syphilis,

perivascular infiltration in the corium is absent, and there is no endarteritis as in syphilis. Dupont and Dubois describe the primary lesion as an epidermic papule of which the centre becomes necrotic and leads to ulceration. Cellular infiltration is limited. In contradistinction, the syphilitic chancre erodes the epidermis and extends more deeply. In secondary yaws large papules are formed by inflammatory infiltration with hypertrophy of the epidermal ridges. In the gummatous stage the essential feature is dominance of the epithelioid elements in the infiltration.

Hasselmann (1955) compared the pathological changes associated with pinta, yaws, and syphilis, and found important differences. In the primary lesion of



Fig. 110.—Primary yaws chancre on foot.
(Dr. L. A. León, Quito.)

pinta no proliferation of the intima or media of the small vessels occurs such as is seen in syphilis. In the later stages of pinta and yaws the vessels are still unaffected or show only minimal endothelial swelling. The "primary" lesion in pinta and yaws is both clinically and histologically identical with the subsequent generalized lesions. This is not the case with syphilis. The lesions of pinta show no superficial erosions, unlike those of yaws and syphilis, and do not become necrotic, as is often the case in syphilis and rather less often in yaws.

Symptoms.—As in syphilis, the symptoms of yaws can be divided into three stages—primary, secondary, and tertiary.

PRIMARY LESION (*madra buba* or "mother yaw") (Fig. 110).—According to Sellards the *incubation period* in experimentally-inoculated yaws in man is three and a half to four weeks; in experimental apes it may be as long as three months. Naturally-acquired yaws is reputed to have, as a rule, a

longer incubation period than the inoculated disease. The primary lesion may appear as a granuloma, or a papule, at the site of inoculation, 1-7 cm. in diameter, and is known as the "frambœsoma." It may develop at the site of some old skin lesion or even at the inner canthus of the eye. It is ordinarily extra-genital, but may be situated on any part of the body: the buttock, thigh, knee, leg, arm, breast, or lip (Fig. 111), but is rare on the scalp. The lower part of the leg is the site of predilection; the breasts of nursing women and the mouths of suckling babies are not uncommon sites. In Moss and Bigelow's large series the genitalia were the seat of the primary lesion in only 1 per cent. In native women it is frequently observed at the bend of the elbow, or on the hip, and is contracted in this situation from carrying children who are infected with the disease. Rarely the primary lesion may be so small as to escape detection; it may be single or multiple, and, in fact, great difficulty may be experienced in differentiating it from allied cutaneous lesions, but, as a rule, it is remarkably persistent, lasting from two to four months, and it may persist for a year or more.



Fig. 111.—Primary yaws sore on lips of Australian aborigine child. (Dr. H. Basedow, Adelaide.)

According to the Jamaican Yaws Commission, the primary lesion is found on the lower extremities in over 70 per cent. of cases. In 39 cases it was found:—

On head, face and neck	1
On upper extremities	„ 4
On genitalia	„ 1
On leg	„ 12
On ankle and foot	„ 21

The lesion, on becoming larger, becomes covered with a yellowish secretion or scab. It is at this stage known as the "mother or master yaw," the "mama pian" of the French. In ordinary locations yaws lesions are not painful, unless firmly pressed.

The appearance of the lesion is preceded by a certain amount of constitutional disturbance. The intensity of the general symptoms varies within wide limits; sometimes they are hardly perceptible, so are not complained of, but usually there is well-marked malaise with rheumatic pains. Occasionally there is severe constitutional disturbance lasting for about a week, with rigor, smart fever (100° to 108° F.), persistent headache, pains—worse at night—in the long bones, joints and loins, and sometimes gastric disturbance and diarrhoea, especially in children. The lymphatic glands in the immediate vicinity become enlarged. During the decline of these constitutional symptoms the secondary eruption

appears. The Wassermann reaction becomes positive three to four weeks after the primary lesion and rapidly grows stronger in titre.

SECONDARY STAGE.—This is ushered in by a fine, light-coloured furfuraceous desquamation. The skin becomes harsh and dry, loses its natural gloss, and here and there patches of desquamation (best appreciated



Fig. 112.—Secondary yaws in a Malay boy. (*W. E. Le Gros Clark.*)

with the aid of a hand lens) are formed. These patches are mostly small and circular; occasionally they are oval, irregular, or form rings encircling islets of healthy skin scattered irregularly over limbs and trunk; sometimes they are almost confluent, the patches coalescing and making the skin look as if it had been dusted over with flour. On the other hand, this

furfuraceous desquamation may be so slight as to be overlooked. In some instances the heaping-up of desquamating epidermic scales produces white depigmented patches, very evident on the dark skin of a negro or oriental.

This patchy, furfuraceous condition of the skin may persist throughout the attack, or may reappear as a fresh eruption at any time in the course of the disease. It has been described by Schöbl and Sellards as "keratoid exanthem" in artificially-inoculated yaws.

Appearance of the yaw (Fig. 112).—When the furfuraceous patches have been in existence for a few days, minute papules appear in them. This very characteristic eruption, from which the disease takes one of its names—*frambæsia* (or *raspberry*)—breaks out three months after the primary lesion. These secondary lesions may vary in size from a pin's head to half a crown and, according to Spittel, begin around the primary sore ("mother and daughter yaw"). The itching is usually considerable. As in syphilis, the eruption may be very pleomorphic; it may be roseolar, or consist of macules with desquamation resembling a squamous syphilide. It may appear on any part of the body, especially in exposed situations and on the anterior surface. The papules occur in groups, the larger appearing to be surrounded by a group of satellites, which has given rise to the various native designations for yaws. Auto-inoculation is probably responsible for the appearance of these lesions in symmetrical fashion, whenever the skin or mucous surfaces come into intimate contact; they are present at the angles of the mouth, in the axillæ, in the anal cleft, and in the inguinal region; in contradistinction to syphilis, they are rarely present on the true mucous surfaces, but often in clusters just inside the nostril. Several of the groups may coalesce to cover a large surface.

The yaw is pushed up from the rete Malpighii through the horny epidermis, which breaks over the summit and splits in radiating lines from the centre, the necrosed segments curling away from the increasing papule. Soon a yellow point appears around a hair follicle, consisting of a cheesy-looking substance which cannot be wiped away, unless undue force is used.

From this stage the papule may either cease to grow, the apex becoming depressed, or may go on to form the typical yaw. In the latter case the lesion gradually grows into a rounded excrescence, the yellow material at the top widening out so as to form a complete cap encrusting the little tumour. The smaller tumours are hemispherical; the larger are more flattened, or even depressed at the centre, possessing everted, somewhat overhanging, rounded edges. Occasionally, though rarely, a big yaw may include an area of sound skin.

The firmly adherent crust which caps and encloses an uninjured yaw is yellowish, granular, blotched with blood-stains and encrusted dirt. Deprived of its crust, the little swelling is seen to be red, generally smooth and rounded on the surface, and oozing pale yellowish serum in which spirochætes may be demonstrated; when inspissated, this serum forms a fresh cap to the yaw, and on microscopic examination is found to be teeming with the organisms. According to size, it stands out anything

from $\frac{1}{4}$ to $\frac{3}{4}$ in. above the surrounding healthy skin. Pus, unless a consequence of irritation, is not, as a rule, found under the crust.

Although the formation of the papules and yaws is attended with much itching, the yaw itself is not at all sensitive; the tumour may be touched, with acid even, without causing pain—a diagnostic point of some importance. Sometimes, as in syphilis, the eruption has a circinate character, the so-called “ringworm yaws.” The itching of yaws lesions is a point of differentiation from syphilis.

The yaw usually attains its maximum development in two weeks. For several weeks longer it remains stationary before beginning to shrink. The crust then thins, shrinks, darkens, separates at the periphery, and at last falls off, disclosing, at the site of the former fungating mass, a slightly

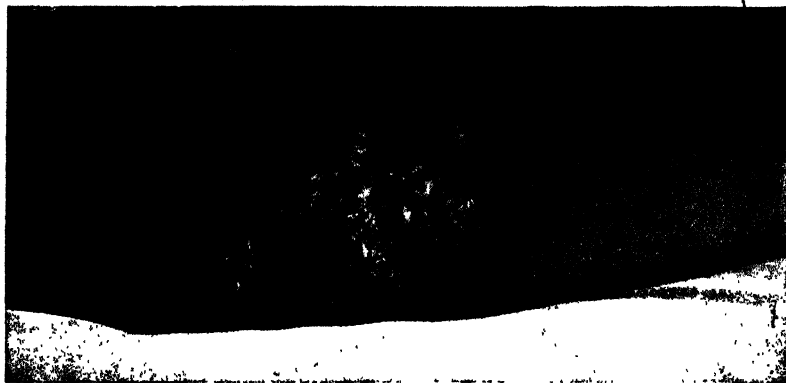


Fig. 113.—Tertiary yaws ulceration on forearm of European.
(P.H.M.-B.)

thickened spot of fairly sound skin, which, though pale at first, may subsequently become hyperpigmented.

Sometimes the secondary rash takes on a papular appearance, when the lesions are known as “acuminate papules.” These are symmetrically distributed over the back, shoulders, arms, elbows and knees, and much resemble a follicular syphilide. Secondary lesions may last from six months to a year. Simultaneously with the eruption, as in secondary syphilis, there may be a uniform, painless enlargement of the lymphatic glands, in the aspirated lymph of which the specific spirochæte may be demonstrated. When the lesions subside, pigmented spots remain, as in secondary syphilis, and are specially noticeable on the palms of the hands.

Lichenoid eruptions.—*Lichen frambæsiæ* (“*Pian datre*”) is a lichenoid generalized eruption of the skin described by Dutch writers in Indonesia. It is a micropapular eruption which is very striking in appearance and is not associated with yaws papules. It is, of course, analogous to secondary lichenoid eruptions in syphilis, and must be distinguished from other lichenoid eruptions, such as lichen ruber planus, lichen pilaris and lichen scrofulosorum. It is now generally recognized as an early secondary manifestation in children and young adults, the

same condition as has been described by Nicholls as "furfuraceous desquamation" and by German writers as the early "frambesiform efflorescence."

The serum of patients in the secondary stage gives marked positive Wassermann and Kahn reactions, and this makes the differential diagnosis from syphilis impossible by these means.

TERTIARY STAGE.—It sometimes happens that the tumours, instead of becoming absorbed, break down and ulcerate, the ulceration, which may last for years, being confined to the yaw itself. In other instances

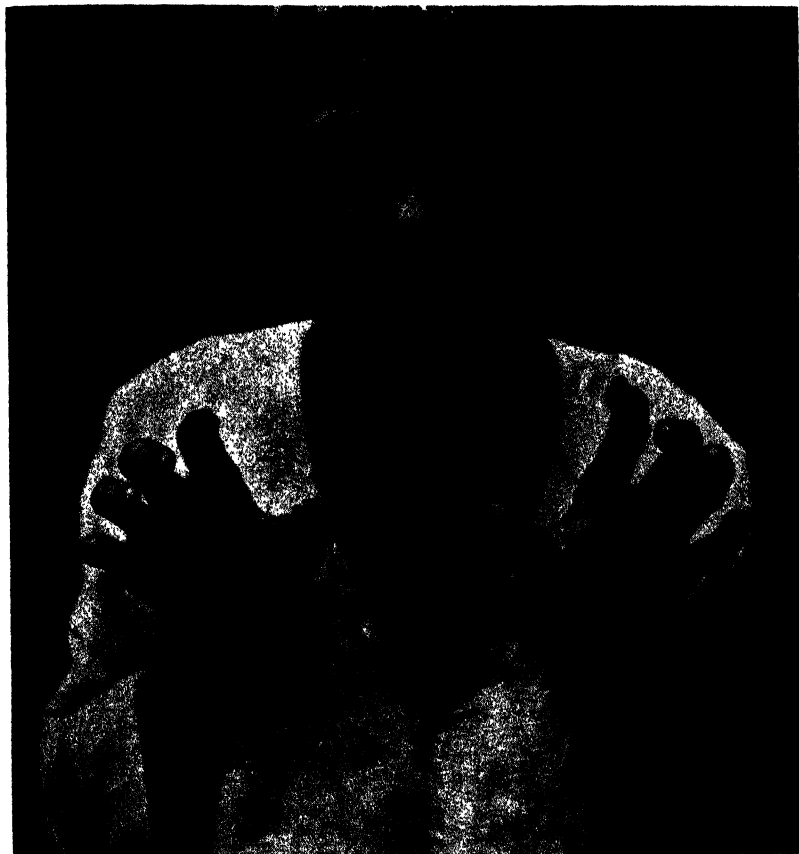


Fig. 114.—Tertiary yaws. Onychia of fingers.
(W. E. Le Gros Clark.)

ulceration goes deeper and extends circumferentially, giving rise to extensive sores with subsequent cicatricial contractions. Such ulcerations occur in about 8 per cent. of cases and may or may not be encrusted. (Fig. 118.) With the development of the deeper and wider forms of ulcera-

tion, the typical lesions of yaws may disappear for a time, or perhaps permanently. In the latter case the ulcers are said to be non-infective. Ulceration of the greater part of the limbs, especially the leg and ankle, may take place. Tertiary manifestations are seldom observed in cases which present late secondary lesions. The serum of these cases gives positive Wassermann and Kahn reactions, but the cerebro-spinal fluid, in cases of advanced ulceration of the nose and other parts of the body, gives a negative reaction with a normal cellular and biochemical picture.

Lesions of the hands.—A scaly condition of the palms of the hands may persist for years. Multiple dactylitis, with uniform swelling of the phalanges, onychia, paronychia, atrophy of the nails, and subsequent deformity, is often observed. (Fig. 114).

Foot yaws ("Dumas," or pink parangi—Ceylon; "crabs," or "crab yaws"—West Indies).—When a yaw develops on the sole of the foot

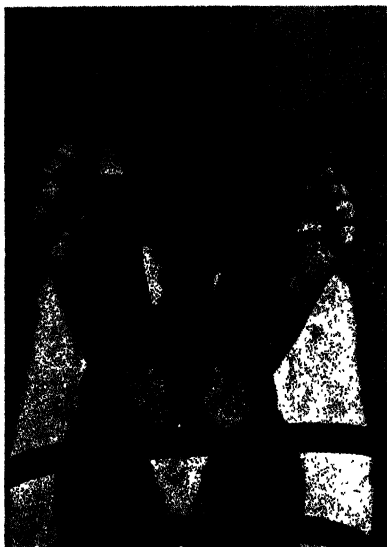


Fig. 115.—Foot yaws, or "crab yaws."
(Dr. J. D. Reed.)

it causes much suffering because it is bound down by the dense and thick epidermis. Spreading laterally under the thick, leathery and unyielding epidermis, it may become large and gives rise to the crab-like gait which distinguishes it. After a time the epidermis over the growth gives way, splitting up in a radiating fashion (Fig. 115). Pressure being thus removed, the yaw fungates, and suffering diminishes. Crab yaws may last a lifetime after infection in childhood. Chesterman suggests that in the foot lesions a fixation point for *S. pertenuis* is formed. A condition known as "clavus" in Dominica results from the healing of these granulomata; the centre of the core drops out, leaving an irregular erosion of the sole of the foot, or there may be deep fissures or cracks. Similar pitting occurs on the palms

of the hands. Dupuytren's contracture (Walters) of the hands is common in both sexes from adolescence upwards in E. Nigeria. It is bilateral and symmetrical. There is no doubt that this is a tertiary manifestation of yaws.

Gangosa (derived from the Spanish meaning "muffled voice"), or destructive ulcerous rhino-pharyngitis (*Rhinatrophia mutilans*) (Fig. 116), which is now generally regarded as a sequel of yaws, usually commences as an ulcer on the soft palate. Slowly spreading, it may make a clean sweep of the hard palate, the soft parts, cartilages and bones of the nose, sparing the upper lip, which is left as a bridge across a great chasm, the floor of which is formed by the intact tongue. A most

offensive odour is given off from the ulcerated surface. The disease may be arrested spontaneously at any period of its progress, and long before such extensive mutilation as that described has been effected; but it is always a longstanding and chronic affair and may linger as an indolent ulceration for years. As a rule, the larynx is spared; but, although phonation may be retained, articulation is seriously impaired. Gangosa occurs at any age,



Fig. 116.—Gangosa in an Australian aborigine. (Dr. H. Basedow, Adelaide.)



Fig. 117.—Goundou, obstructing vision. Ivory Coast. (London School of Hygiene and Tropical Medicine.)

but is rare in young adults, though Leyes states that in Guam he has seen it in children of 3, 4, and 9 years of age. It is very common in parts of the West Indies (Dominica, 60 cases in a population of 2,000), Guam (1.5 per cent. of the population), the Carolines, Fiji, Ceylon, British Guiana, and West, Central, and East Africa. It is often found associated with the bone lesions of yaws.

Goundou, *Anákhre*, *Attié* ("Gros Nez").—In 1882 MacAlister drew attention to what were termed the horned men of Africa, and in 1887 Lamprey gave further details illustrated with drawings. The natives call the disease goundou and anákhre (Fig. 117). Later observations show that it has a wide distribution in Central Africa and South America, and has been observed also in Martinique, Malaya and China, and that a similar disease occurs in the larger apes, chimpanzees, and baboons. An ancient Inca skull from Peru, described by Letulle, shows the characteristic lesions of goundou.

Stannus and Hamerton have shown that in the apes the hyperostosis is probably the after-result of osteitis cystica.

Goundou usually commences during childhood, although adults may be attacked. The earliest symptoms are severe and more or less persistent headache which, after a time, is associated with a sanguino-purulent discharge from the nostrils, and formation of symmetrical swellings the size of a small bean at the side of the nose. Apparently the swelling affects the nasal process of the superior maxilla. The cartilages are not involved. After continuing for six or eight months, the headache and discharge subside. The paranasal swellings persist, and continue slowly and steadily to increase until in time they may attain the size of an orange, or even of an ostrich's egg. As they grow, the tumours, encroaching on the orbits, may interfere with the line of vision and finally destroy the eyes. In severe cases there is a general diffuse hyperostosis of the anterior part of the maxilla. There is no pain in the tumours themselves. The superjacent skin is healthy and freely movable. The tumours are oval, with the long axes directed downwards and slightly from within outwards (Fig. 117). The nostrils are bulged inwards and more or less obstructed. The hard palate is often affected, resulting in the most hideous deformity. General glandular enlargement may be noted. Trauma seems to predispose to the development of goundou.

A case of goundou associated with tertiary syphilis was described in London by Sharpe. The patient had never been in the tropics. Similar goundou-like swellings have been reported in bejel (Arab syphilis).

Cases of goundou in Jamaicans invariably give a positive Wassermann reaction.

The bony outgrowths, not necessarily bilateral, are attached to the nasal bone and nasal process of the maxilla, but, according to Botreau-Roussel and Clapier, they are not entirely confined to this region; a similar hyperostosis may co-exist on the tibia, upper or lower jaw, forearm, femur, or clavicle. There is a general opinion at present that goundou is a systematized hypertrophic osteitis connected in some way with yaws. Botreau-Roussel was able to observe the gradual development of goundou, on the French Ivory Coast. A little girl of 1½ years developed yaws, later on osteitis in the long bones and finally the involvement of the maxillary bones producing goundou took place.

The bony changes of goundou consist of hyperostosis, which may be limited to the ascending or nasal processes of the superior maxilla, or be more widespread and affect the other bones of the skull as well, with an ever-present tendency to the formation of bosses of overgrowth and to the obliteration of adjacent cavities. The underlying



Fig. 118.—Gummatous osteitis of radius and ulna in Yaws. (Dr. C. J. Hackett.)

pathological process is an osteo-periosteal dyscrasia and the end-result is the production of finely-porous bone. Benjamins considers the possibility that infections of the nasal cavities or paranasal sinuses may spread through the suture nasomaxillaris and produce periostitis resulting in ossification. No one has, as yet, demonstrated spirochaetes in the osseous tumours.

As yaws and syphilis are so closely allied, it might be expected that similar lesions might be found in the generalized osteitis of syphilis, but there appears to be very little evidence of it. There is very little difference between the bony changes of goundou and those which have been called *leontiasis ossea*, and, according to Stannus, hyperostosis of the facial bones has also been recorded in Paget's disease—*osteitis deformans*. According to modern knowledge, it seems possible that goundou is more akin to *osteitis fibrosa*, due to interference with the



Fig. 119.—Distortion of fingers in tertiary yaws.



Fig. 120.—Tibial periosteal nodes, ulcers, and deformity of phalanges in yaws.

bony metabolism and an endocrine disorder, and it may well be that in this instance yaws constitutes the non-specific factor acting on an ill-fed native child population. Goundou-like swellings in horses, monkeys and young pigs ("cachexie osseuse") point to osteitis fibrosa as the initial stage of this condition and all changes between cystic disease of the bones and hypertrophic exostosis can be traced in a series of skulls.

Treatment consists in incising and displacing the periosteum and chipping away the bony outgrowth with a chisel. Early cases, according to Botreau-Roussel, yield to intravenous and intramuscular injections of neosalvarsan, four or more injections being necessary before improvement is observed. This observer operated with success upon 113 out of 130 cases observed on the French Ivory Coast and the reader is referred to his monograph (Masson et Cie., 1925) for further information.

Periostitis, osteitis and epiphysitis (Figs. 118, 119, 120).—Circumscribed painful periosteal nodes are frequently found on the anterior aspect of the long bones, especially the radius, ulna, and tibia. The swellings are hot and exquisitely tender, and the superjacent skin is tense and stretched. After

the subsidence of the acute stage, hard, firm periosteal nodes remain. A diffuse osteitis may result in a sabre-shaped deformity of the long bones, especially the tibia and occasionally the arms and fingers. A rarefying process is also at work, for such bones are subject to spontaneous fracture with resulting malunion, accidents which are common in districts in which yaws is endemic. Hackett, who has studied the sabre-shaped tibiae of the aborigines of Australia, believes that syphilis does not occur among these peoples, and that the bone lesions are due to yaws. Colloquially known as "boomerang leg," the deformity is an antero-posterior curvature below the knee with a forward convexity; occasionally there are bosses of localized periostitis. Radiographs show that areas of

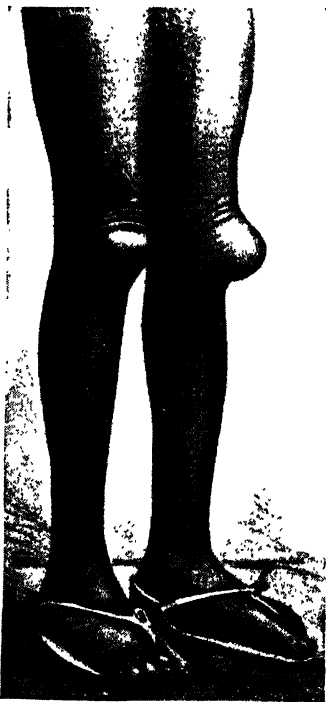


Fig. 121.—Juxta-articular nodules.
(Photo: Dr. Watt.)

rarefaction appear early, and the bone becomes deformed. Gummatous lesions were also found by Hackett (Fig. 118). The appearances depend upon the severity of the initial lesion and the time which has elapsed since the onset of the disease. Other lesions of yaws, including gangosa, have been noted in Central and Northern Australia. A chronic periostitis of the clavicle is frequent in Fiji. These bone changes are accompanied by intense rheumatic pains, and have received distinctive names, such as "sasala."

Juxta-articular nodules.—Fibrotic tumours situated over the olecranon, the lower end of the femur, and in other situations on the long bones, are regarded as a tertiary phenomenon of yaws, and Sobernheim has demonstrated spirochaetes in them by the silver-impregnation method of Levaditi. Formerly they were regarded as constituting a disease *sui generis*, but those cases which have been investigated invariably give a positive Wassermann reaction. Originating subcutaneously, these nodules may reach the size of a small orange (Fig. 121). Chambers in Jamaica found these nodules in endemic yaws in rural areas and in only nine children under fourteen years of age.

Tiny nodules may be felt as early as one to two years after infection, but they usually appear after a lapse of 15–40 years. It is also pointed out that, when bone lesions are present, the nodules tend to form in their vicinity. They are remarkably painless, and very rarely ulcerate or suppurate. Juxta-articular nodules are generally multiple, usually in the neighbourhood of the joints, but, according to Steiner, may also occur scattered over the body. Similar lesions were first described by Jeanselme in 1899 in tertiary syphilis, and since that time the *Spirochaeta pallida* has been

isolated from them (Hu and Frazier), while Hudson found the same nodules in "bejel," the non-venereal syphilis of the Arabs, among whom they occur in 2·1 per cent. of the adult male population and are known locally as "rik." According to Frontoynant and Girard, they often contain uric-acid crystals. In Africa they are apt to be mistaken for *Onchocerca volvulus* cysts.

Skin lesions.—Healing of subcutaneous gummata is frequently followed by depigmentation of the skin, resulting in light-coloured or leucodermic patches, especially visible in native races. A macular depigmented exanthem limited to the hands, wrists, feet and ankles is pathognomonic of yaws and was first described by Ziemann as "melung."

The radiographic appearances of the bone lesions of yaws in Uganda have been intensively studied by Hackett. Apart from the absence of osteo-chondritis in yaws, there is probably no bone lesion that occurs in one disease that may not be observed in the other.

Secondary cases show focal rarefaction in the cortex, periosteal deposits in which rarefactions also occur. Although in many lesions the bones finally return nearly to normal, sometimes cortical thickening and bone expansion result and may lead to increased convexity of its anterior profile (sabre tibia).

In secondary bone lesions, and to a less extent in tertiary lesions, spontaneous resolution takes place in a few months. Next to the tibia the ulna is most frequently involved; next in frequency are the hand, and lastly the footbones and radius. No changes are found in joints. Periosteal deposits indicate active periostitis: cortical rarefactions and rarefying osteitis. Periosteal deposits can be regarded as an osteoperiostitis.

After effects.—Contractions resulting from scar tissue may lead to partial ankylosis of joints, in severe cases to the destruction of lymph-channels and to the production of elephantiasis in the affected limb.

Synovitis.—Chronic synovitis, analogous to that of tertiary syphilis often associated with bone lesions, and, it may be, with disorganization of the joint, has been recorded.

Ganglion and other lesions.—The frequency of tenosynovitis and ganglion-formation in the region of the wrist was noted by Graham, Moore, and other observers. These ganglia are usually associated with tenosynovitis and, as extra proof of their origin, they both respond in a remarkable manner to treatment with neosalvarsan and penicillin. Stricture of the mouth due to tertiary yaws has been recorded.

The general health.—Except during the initial fever, or during one of the recurring febrile relapses, the general health is not, as a rule, affected. Occasionally, however, there are debility and cachexia; or there may be enlargement and tenderness of the lymphatic glands. In other instances rheumatic pains may be very severe.

Immunity.—After the subsidence of the secondary stage immunity is produced, but Sellards and Goodpasture demonstrated that this is relative only, for they successfully reinoculated with the disease patients who had undergone a course of salvarsan treatment. Apparently, saturation of a community with yaws virus produces a relative immunity to syphilis. On these grounds may be explained the well-authenticated

fact that syphilis is absent amongst the Polynesians of Fiji, Tonga and Samoa, in whom yaws was especially prevalent. Formerly Fijians were in the habit of inoculating their children against yaws to protect them from subsequent attacks. As far as accurate experiments have gone, immunity in syphilis is acquired much earlier than in yaws. Now that yaws has been eliminated in Suva and surrounding districts, the third generation of Fijians reared in these surroundings is becoming infected on an increasing scale with syphilis, and the congenital form in children has been observed (Clinton Manson-Bahr).

Duration and recurrences.—Yaws lasts for weeks or months or years, its duration depending on general health, idiosyncrasy, hygienic conditions, and the treatment. Mild cases in healthy subjects terminate in about six weeks, though the average duration of an attack is estimated at about one year. In other instances, especially in the debilitated, the disease runs on for months, successive crops of eruption being evolved. Sometimes these recurrences may stop short at the stage of desquamation, or at the papular stage, or they may proceed to the formation of typical yaws. They are usually preceded by feverishness, pains in the bones and joints, and the successive crops may either be limited and partial in their distribution, or general.

Mortality.—Although in the literature reference is made to deaths from yaws, yet, judging from the statistics collected by Nicholls, the mortality must be small indeed.

Diagnosis.—A painless, insensitive, larger or smaller, circular, encrusted red, granulomatous excrescence occurring in an endemic district is almost certainly yaws. The most important point about yaws, both in diagnosis and in ætiology, is its relationship to *syphilis*. Both diseases may occur in the same individual (Powell cites two cases, and Charlouis two, of syphilis supervening on yaws); and antecedent syphilis certainly does not confer absolute immunity to yaws, nor antecedent yaws to syphilis. The serum in both diseases gives a positive Wassermann reaction. Yaws may die out in a community, as in British Guiana (Daniels), yet syphilis remain; yaws may be universal in a community, as in the Fijians, Tongans and Samoans, and yet true syphilis, whether as an acquired or as a congenital disease, be, until recently, unknown. In yaws, Hutchinson's famous syphilitic triad—the characteristic notched teeth, nerve deafness, and interstitial keratitis—are absent.

Table IX shows the main points of differentiation.

TABLE IX

YAWS	SYPHILIS
Not congenital.	Congenital.
<i>Primary sore</i> —extragenital.	<i>Primary sore</i> —usually genital.
<i>Secondary stage</i>	<i>Secondary stage</i>
(a) Typical yaw pathognomonic; furfuraceous desquamation and plantar lesions characteristic.	(a) Seldom imitates the frambœsia of yaws.

TABLE IX *continued*

<i>Secondary stage</i>	<i>Secondary stage</i>
(b) Mucous membranes not affected.	(b) Mucous membranes affected.
(c) Itching common.	(c) Itching rare.
(d) Alopecia unknown.	(d) Alopecia may occur.
(e) Eyes unaffected.	(e) Iritis common; choroiditis and retinitis rare.
<i>Tertiary stage</i>	<i>Tertiary stage</i>
(a) Visceral lesions absent.	(a) Visceral lesions occur, e.g., pericellular cirrhosis, gumma of liver, kidney.
(b) Nervous system not usually affected.	(b) Nervous system liable to infection: tabes, G.P.I.
(c) C.S. fluid always negative Wassermann (Fischer; Turner, Saunders and Johnson).	(c) C.S. fluid usually positive Wassermann.
(d) Blood-vessels: no endothelial proliferation as in syphilis.	(d) Endarteritis obliterans of viscera—cerebral thrombosis.
(e) Late manifestations: condylomata; crab yaws; hyperkeratosis.	(e) Late manifestations: condylomata; rupia.
Yaws better resisted. Constitutional disturbance slight; great exuberance of eruption and cheloid scarring.	Syphilis attacks constitution, affecting the vital structures.

Secondary yaws may have to be differentiated from bromide rashes.

Serological reactions.—De Mello and Krag (1955: W.H.O.) have reported the results of the V.D.R.T. (Venereal Disease Reference Test of Harris)¹ in 6,000 untreated and treated cases of yaws in all stages seen in Thailand during an anti-yaws campaign (1951–53), their conclusions being based on the serological examination of 3,632 cases. In early untreated cases 97.5 per cent. of sera gave a positive reaction up to a dilution of 1 in 256, irrespective of age of patient. In the next stage, manifested by palmar and/or plantar hyperkeratosis, a somewhat lower level of seropositivity was found (18 per cent. of 544 cases gave a negative result). Analysis by age groups showed that at this stage of the disease the serological reaction in the younger age groups was invariably strongly positive. There were 342 cases which had reached the stage of bone and joint lesions or pains, and of these 25.7 per cent. gave a negative reaction.

TREATMENT

1. Salvarsan, neosalvarsan (Neoarsphenamine²).—Except where much bone destruction has taken place, salvarsan, or better still its more recent and more soluble derivatives, has a curative effect upon yaws in every stage of the disease. The most generally used drug at the present time is neosalvarsan (neoarsphenamine). It is given intravenously to adults, and, if possible, to children; or intramuscularly (0.4 grm. dissolved in oil, into the buttock). The more urgent symptoms yield much more rapidly than do those in syphilis, and relapses are not so common. Since

¹ The most sensitive equivalent of the Kahn test.

² Throughout this account the terms arsphenamine and neoarsphenamine are given as the American equivalents of salvarsan, neosalvarsan, etc.

the introduction of salvarsan the natives of the Congo dislike being treated until the secondary rash is well out. For adults the intravenous dose advocated is 0.6-0.9 grm.; for young adults 0.6 grm., for children up to ten years of age 0.3 grm., and for children under two years, 0.1 grm.

II. Bismuth.—The successful treatment of syphilis by Fournier with sodium-potassium-bismuth tartrate led to the adoption of a similar method in yaws. The considered opinion of workers is that none of the many bismuth preparations can be said to take the place of the synthetic arsenicals in African yaws and syphilis. The most active form appears to be the *sodium tetra-bismuth tartrate* in both secondary and tertiary yaws.

All preparations act more efficaciously when given in the early stages. Injections should be made deep into the subcutaneous fascia, and occasionally some induration and abscess-formation may result with *Sobita*—a soluble form of sodium-bismuth tartrate, but this has now been superseded by penicillin. Since 1924, over a million cases have been treated in Tanganyika.

III. Penicillin.—As first established by Lourie and Collier (1943) penicillin has a remarkable specific action on the syphilis spirochæte and this knowledge has been used in the treatment of yaws, where, as far as can be at present ascertained, the results of penicillin are even more satisfactory and are readily appreciated by the native population. A number of papers have appeared in latter years, mostly by American workers in the



Fig. 122.—Secondary Yaws. (Dr. C. J. Hackett.)

A. Showing papillomata in various stages of activity.

B. After penicillin treatment. The absence of scarring is well shown.

Pacific war zone. The results are most striking in the primary and secondary stages. Thus Whitehill and Austrian (1944) described the treatment of 41 primary and secondary cases in Fijians, in whom spirochætes were demonstrated by dark-ground illumination. Thirty were under fifteen years of age. Penicillin was injected intramuscularly in doses of 15,000–30,000 units at intervals of 3–4 hours to a total dosage of 100,000–2,400,000 units. All lesions were completely healed in three weeks and spirochætes disappeared from the lesions after 16 hours. Lofgren (1944) reported a case in a European who received $1\frac{1}{2}$ mega units and by the twelfth day all lesions had healed. Findlay, Hill and Macpherson had a similar experience in West Africa and witnessed complete healing of a primary yaw in $6\frac{1}{2}$ days. Further reports show a remarkable agreement, such as those of Tompsett, Kauer, and Guimaræs. From South America confirmatory evidence is forthcoming, but with smaller doses. In seven patients all external evidence of yaws disappeared between the twelfth and forty-fourth days of treatment and serological reactions became negative on the sixtieth day (da Cunha, Leão and Guimaræs, 1945). Flock and de Lajudie give 100,000 Oxford units of sodium penicillin in sterile olive oil by intramuscular injection in the secondary stage. The individual dosage is 1 ml. of oily suspension containing 10,000–15,000 units daily for seven days or longer. Ghestin in Gabon (1956) gave a single injection of benzathine penicillin up to 1·2 mega units to 69 children with primary and secondary yaws and commented on the rapid disappearance of the lesions. (Fig. 122, A & B).

Procaine penicillin is superior because it is slowly absorbed, and therefore injections can be made much less frequently. By this method adequate serum concentration can be maintained above 0·03 units per ml. for a period of 72–96 hours. Procaine penicillin is given in arachis oil, jelled with 2 per cent. aluminium monostearate in the following schedule: on the first day injection of 4 ml. procaine penicillin (1·2 mega units), then one daily for six additional days, or 2 ml. twice a week for three weeks. Tavares (1950) in Brazil finds this method much superior to arsenicals in 75 cases, and 40 were cured in an average of 27·12 days; average total dosage was 3 mega units. Spirochætes were not found six days after commencement of treatment. Penicillin aluminium monostearate (P.A.M.) is the preparation recommended by W.H.O. (1953). It is now possible by using a repository preparation of penicillin to maintain an effective blood level for 8 days after a single intramuscular injection which suffices to cure 80 per cent. of all cases. The preparation is a microcrystalline procaine benzypenicillin in oil with 2 per cent. aluminium monostearate; the optimum standard is under 3 years, 600,000 units in 2 injections, 3–10, 1,200,000 units in 2 injections, 11 onwards, 2,400,000 units in 2 injections, at seven days interval.

IV. Other antibiotics.—*Chloromycetin* (chloramphenicol) has proved satisfactory (Findlay and Ampofo). *Aureomycin* also is effective in cases resistant to penicillin (Lins, 1950) in doses of 0·75–1·5 grm. for 3–4 days in children. For adults 2 grm. is given daily for five consecutive days. *Terramycin* (oxytetracycline) (Loughlin and Joseph, 1951) in the treat-

ment of tertiary yaws is even more effective than procaine penicillin in the following dosage: 3 grm. on first ; 2 grm. on second and third days (total 7 grm.). Sixty-five cases were observed for two months on terramycin by the mouth. Clinical cure is effected in 6-16 days. In over 80 per cent. spirochætes could not be demonstrated 48 hours after treatment had commenced. Wet secondary plantar lesions were healed in 11 days. It was also injected by the intramuscular route daily for five days. The drug was dissolved in sterile water: 250 mgm. in 5 ml.

Prophylaxis resolves itself into the adoption of measures to prevent contagion. These are the isolation and segregation of the affected ; the dressing and treatment of wounds in the hitherto unaffected ; the application of antiseptic ointments to yaws sores, so as to obviate the diffusion of spirochætes by flies ; the purifying or destruction by fire of houses or huts notoriously infected ; the prevention of pollution of bathing-water by yaws discharges ; and, especially, the prompt treatment of the infected by salvarsan, bismuth, penicillin or terramycin.

CHAPTER XXXVI

MYCETOMA, BLASTOMYCOSIS AND OTHER FUNGUS INFECTIONS

Synonyms.—Mycetoma; Madura Foot; Pseudactinomycosis; Maduromycosis.

Definition.—Mycetoma may affect any part of the body exposed to trauma, and it is not rare in other parts than the foot and hand, although it occurs most frequently in these two extremities. It is extremely uncommon in the internal organs. Visceral mycetoma has, however, been applied, mistakenly, for various forms of pulmonary mycoses not related to madura foot, as for instance for pulmonary aspergillosis. Madura foot, or maduromycosis, is the term applied to the fungous disease as it affects the feet. The disease is not necessarily fatal *per se*, but, according to Abbott, when death occurs, it is attributable to malnutrition.

Geographical distribution.—In India, mycetoma is endemic in widely scattered districts, although whole provinces, as that of Lower Bengal, enjoy an almost complete immunity. It appears to be acquired only in rural districts, the inhabitants of the towns being exempt. Among the more afflicted districts may be mentioned Madura—hence the name “Madura foot” by which mycetoma is often known—Delhi, various places in the Punjab, Kashmir and Rajputana. Africa appears to be chief home of mycetoma, extending from the East across S. Sudan and French Equatorial Africa to the West Coast, down through Nigeria to the Belgian Congo. It also occurs in Madagascar, Cochinchina, Italy, the United States, and South America.

Ætiology.—Mycetoma may be caused by many species of “fungi.” The classification of Chalmers and Archibald (1916) of the mycetomas is generally followed. They are divided into two groups: (1) The *Actinomyces*, caused by actinomycetes and (2) The *Maduromycoses*, caused by true fungi, and, in accordance with this idea, the terms actinomycetoma and maduromycetoma have been proposed, but have not been generally adopted.

The causative micro-organism of mycetoma is seen in the lesion as a small compact colony or “grain” of various sizes and colour, according to the species of causative “fungus.”

The mycelium in the grain is arranged in radial formation and, in the case of some of the fungi, the peripheral part is formed of large, thick-walled cells usually known as *chlamydospores*. Surrounding the grain, in many species, is a layer of hyaline, eosinophil material, often drawn out into club-like bodies forming a kind of corona on the grain, which is more or less characteristic of the species of micro-organism. These hyaline formations, which are common also on other species of fungi, notably *Sporotrichum* and *Aspergillus*, represent a reaction by the host which is probably defensive.

The maduromycoses, which are caused by true fungi, possess grains composed of coarse, septate mycelium, whereas the grains of the actinomycetes show only very slender non-septate hyphæ, usually not exceeding $1\ \mu$ in diameter—which represent the characteristic bacillus-like *thallus* of the actinomycetes. (Fig. 123).

A great variety of fungi have been isolated from actinomycetes and maduromycetes in tropical countries so that the terminology has become confused and the task of weeding out synonymous names has been considerable.

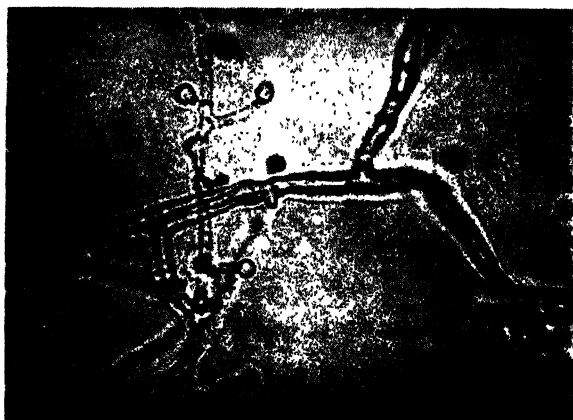


Fig. 123.—Aleurospores of *M. mycetomi*.
(Peter Abbott.)

Therefore, in accordance with the researches of Mackinnon (1954), Abbott (1956) and J. T. Duncan, the older classification of the maduromycoses has been abandoned.

Mycetoma with black grains may be due to *Madurella mycetomi* (with numerous synonyms), *M. grisea*, and *Phialophora jeanselmei* (*Torula jeanselmei*).

The species *Madurella mycetomi* of Laveran was originally based on characters of the parasitic grain and not on the fungus in culture. The original name is not accepted by Mackinnon, by da Silva Lacaz and by Vanbreuseghem. The second-named has proposed it should be called *M. tozeuri* (Nicolle and Pinez 1912). Now, however, the term *Madurella mycetomi* is generally accepted as correct. The proposals of Abbott (1955) have brought in all the known species of *Madurella*, except *M. grisea*, into the synonymy of *M. mycetomi*.

Abbott (1955) described for the first time a conidial form of *M. mycetomi* which developed in the depth of a soil extract agar medium and showed that the species *Glenospora khartoumensis* (Chalmers and Archibald 1916) is, in fact, *M. mycetomi*. As synonyms Mackinnon now includes the following: *M. tozeuri*, *M. tabarka*, *M. americana*, *M. ikeda*, *M. tackawanna*, *M. oswaldoi*, *M. viridobrunnea*, and *Glenospora khartoumensis*.

I. CARTER'S BLACK MYCETOMA (*M. mycetomi*)

This is found mainly in tropical Africa, India, other Asiatic countries, and also in parts of N. and S. America. There and perhaps also in India the geographical distribution of *M. mycetomi* and *M. grisea* may overlap.

The parasitic grains of *M. mycetomi* consist of a radially-spreading septate and branching mycelium, measuring 1–5 μ in diameter with chlamydospores up to 25 μ . The actual grains are dark-brown or black and measure 1–2 mm. in diameter. They are also hard and brittle. This fungus grows readily on Sabouraud's medium. Abbott has shown that the grains remain viable for three months or longer. In culture *M. mycetomi* can utilize glucose, maltose and galactose, but not sucrose as sources of carbon, but as sources of nitrogen it makes use of potassium nitrate, ammonium sulphate, asparagin and urea.

Madurella grisea Mackinnon may be the predominant form in the geographical range of *M. mycetomi* in S. America.

The parasitic grains of this species differ from those of *M. mycetomi* in the unpigmented central part surrounded by a blackish, cortical zone. In this marginal zone the mycelium is embedded in a brown cement. On culture *M. grisea* is unable to utilize sucrose, in addition to other sugars already mentioned.

The colonies on glucose-agar are hard, creased and folded, almost black in colour, and covered with grayish-white pulvulence.

In Czapek's medium puff-ball colonies are formed with dark centres.

Hyphae are either cylindrical, measuring 2–3 μ in diameter, or moniliform and thicker, 3–4 μ . They are branched and septate and give rise to more slender, almost colourless, hyphae.

Allescheria boydii appears to be widely distributed and causes a mycetoma with yellowish-white grains, and has been studied by Courtois and colleagues (1954) in the Congo. *Cephalosporium falciforme*, which is somewhat similar, has been isolated by Carrión in Porto Rico. (*Monosporium apiospermum*, a common cause of mycetoma, represents the imperfect or conidial form of *A. boydii*. *Indiella mansonii*, one of the numerous species created by Brumpt, appears to have been *M. apiospermum*.)

II. MADURA FOOT.—VINCENT'S WHITE MYCETOMA

The organism is *Streptomyces madurae* (formerly *Actinomyces madurae*, Vincent, 1894). It has been found in Algeria, Abyssinia, Somaliland, Cyprus, India, Argentina and Cuba. The species is monomorphic and constant. The grains may reach a size larger than that of any other species. They are whitish-yellow, sometimes with a pink tinge. The central part of the grain may be hollow and contain scant, loosely and irregularly packed filaments which radiate. Clubs are usually observed. They are elongated, up to 25 μ , tape-like and sometimes branched. The ends may be pointed and they usually stain pink with eosin. (*S. madurae* is synonymous with *Actinomyces brumpti*, and *Discomyces bahiensis*.)

III. YELLOW-GRAINED MYCETOMA

The fungus is *Streptomyces somaliensis* (or *Nocardia somaliensis*), Brumpt, 1906, and has been extensively studied by Abbott (1956) in the Sudan.

It occurs also in Abyssinia, West Africa, São Paulo—Brazil, in Egypt, commonly in the Sudan and Somaliland. (The fungus appears to be identical with *Indiella somaliensis* of Brumpt and at one time the disease was called Bouffard's white mycetoma.) On Krainsky's medium it forms a thin, smooth pellicle and a short, light, ochreous aerial mycelium. On glucose peptone, agar cream-coloured pellicles are produced and the culture may become brownish or blackish.

The mycelium is non-segmented with some chlamydospores about $1\ \mu$ in diameter. The aerial conidia are $1.25\ \mu$ typical of the genus *Streptomyces*.

Peptone and asparagin are assimilated, but ammonium sulphate, potassium nitrate and urea are not. The grains are yellowish, $1.25\ \text{mm}$. in diameter, round, oval and compact. They are composed of a matrix of amorphous material showing slits and embedded on this the filaments of actinomyces are easily observed. Inoculations of mice and guineapigs have proved unsuccessful.

IV. RED GRAINED MYCETOMA

This form has been shown to be widespread in the Sudan by Abbott. In its gross pathology it is similar to the others, but it is of greater virulence.

The organism is *Streptomyces pelletieri* (Laveran, 1906) or *Nocardia pelletieri*. It is found in the Sudan, Senegal, Nigeria, India, Arabia and other countries. It produces (according to Mackinnon) slow growth in all media. On Krainsky's medium it forms hard red, purple, adherent colonies. There is a poor growth on Czapek's medium.

Non-segmented branched vegetative mycelium is produced with some swellings up to $1\ \mu$ in diameter. No conidia are observed. The organism is not semi-acidfast and stains well by Gram's method. On basal medium with asparagine only glucose favours growth. Peptone and asparagine are utilized; urea and potassium nitrate are not.

The parasitic grains are deep red in colour, rather small, and rarely reach $1\ \text{mm}$. in diameter. They are very irregular in shape and have smooth or denticulate edges. Some are seen to be enveloped by a refringent hard pellicle.

V. NOCARDIA BRASILIENSIS (LINDENBERG, 1909)

The general term *Nocardia* is reserved for the semi-acid fast species. The species is found in Mexico, Brazil and Venezuela.

It is a rapid growing actinomycete and forms on Krainsky's medium heaped-up colonies with membranous consistency and marked furrows. The colour varies from pale ochre to orange or red ochre. Scarce aerial mycelium is formed in Krainsky and more abundantly in Czapek's media. The cultures produce an earthy odour.

A non-pigmented mycelium prevails. All strains are semi-acid fast and stain well by Gram.

On basal medium with asparagin, glucose and galactose are utilized, but maltose, sucrose and lactose are not.

The parasitic grains are irregular, of moderate size, built up by lobules without clubs. Mice inoculated in the peritoneum developed abscesses,

1 to 3 mm. in diameter, in pancreas omentum and in between the liver and diaphragm.

VI. *NOCARDIA ASTEROIDES* (EPPINGER, 1891)

These cultures were isolated by Fonseca in Rio de Janeiro and in Montevideo. On Krainsky's medium it produces a soft, inconsistent, creamy growth which acquires some orange and rose colour. On liquid media an inconsistent veil is formed.

The cultures are similar to those of *N. brasiliensis*. The mycelium may be segmented.

This fungus has no proteolytic activities and does not hydrolyse starch and can utilize all the nitrogenous compounds.

When inoculated into mice it produces small abscesses similar to those described above.

In general, with the exception of I and II, these cases do not conform to the classical picture of Madura foot. Instead the concavity of the plantar arch and instep are preserved and the swelling is mostly on the dorsum of the foot. The thin, serosanguinolent discharges from the sinuses contain yellowish-white grains, about the size of sand grains. They are about 0.5–0.4 mm. in diameter, irregular in outline and sometimes dented. There are no club-formations, but only an irregular cosmophile fringe on the surface of the grain.

Epidemiology.—It is probable that in Africa and India penetration of the skin by thorns is the commonest cause. Abbott found them embedded in the tissues at operation in seven subjects of yellow and two of black mycetoma. As the disease takes months to develop, it is not surprising that most do not appreciate the causal connection between thorns and their tumours. There is, however, no evidence that the organisms are saprophytic on thorns, which act as mechanical carriers. The grains of mycetoma can withstand drought for prolonged periods and it is probable that they can remain dormant, but viable, until the rains fall. With the moistening of the ground they may develop as has been observed on soil-extract agar with the production of numerous aleurospores which may transmit the infection to man. In the Sudan there is close correlation between the incidence of the disease and rainfall and it would seem that it is this and the type of climate which determines the ecology of the soil and thus the presence of organisms causing mycetoma.

Madura foot is by no means such a rare disease as is generally supposed. Abbott (1956) relates that in a 2½ year period in Sudan, 1,231 cases were reported admitted for hospital treatment. The admissions for mycetoma per thousand in the central belt of the Sudan is high. It is 5.1 at Khartoum and 9.8 at Ducim, and 11.8 at Wad Medani.

Symptoms.—Whatever the colour of the grains or species of fungus, the clinical course remains remarkably uniform. The first sign noticed is a painless swelling, usually, but by no means invariably, on the sole of the foot. Abbott has shown that in yellow mycetoma it is ill-defined, while in black mycetoma, it takes the form of a clearly-defined, painless nodule in the subcutaneous tissues. The conception of an incubation period can hardly be applied.

Probably the fungus commences to develop as soon as it is implanted—sometimes, too, it may happen that a period of 10 years may lapse before the patient has been sufficiently incommoded to seek treatment. In the meantime, the growth continues slowly and inexorably. It may be a very long time before the deeper tissues are invaded, but the granuloma spreads inwards, invading the bones. Nodules, at first paler than the surrounding skin, form on the surface, revealing the mouths of the sinuses. From there a purulent fluid is discharged, containing the characteristic coloured grains of the fungus (Fig. 124). With all this the relative lack of pain is most remarkable and it is only when the foot or leg has been rendered

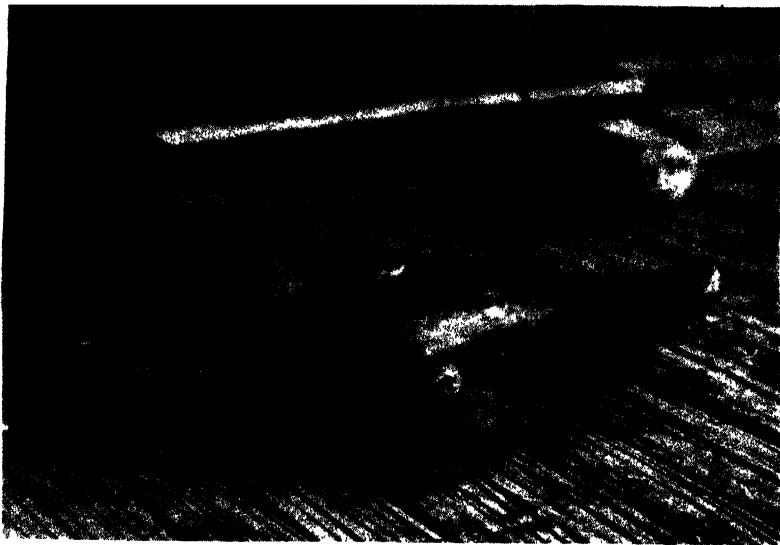


Fig. 124.—Madura foot. (Dr. L. A. León, Quito.)

quite useless that the patient suffers appreciably. No fever or other systemic effects accompany mycetoma of however long standing, large or destructive the lesion may be, unless secondary bacterial infections supervene.

The regional glands may sometimes be involved and the causal fungus has been found in them by Abbott in six cases. Those visible lesions are situated in less disabling sites. Back, buttocks or thigh may remain well-nourished and in good condition. In the majority of cases it is the effects of *inactivity* and economic loss which lowers the patients' vitality.

An important feature, not sufficiently emphasized in text-books, is the fact that sinuses that are diagnostic may be late in appearing. The interval may be as long as six years. As the foot enlarges, the leg commences to atrophy from disuse; so that in advanced disease, an enormously enlarged and mis-shaped foot, flexed or extended, is attached to an attenuated leg consisting of little more than skin and bone.

The intraosseous mycetoma is primarily a fungous tumour occurring in the metaphysis of a long bone, usually the upper end of the tibia. All the cases of this variety have been in boys under 18 and all were caused by *M. mycetomi* (Fig. 125).

The patient usually complains of dull, aching pains in the affected part. Examination reveals widening of the bone at the site of infection without involvement of the skin. It is probable that in these cases the infection



Fig. 125.—X-ray of Madura foot. (Infection of metatarsals.)

is blood-borne. Periosteal tumours appear in all varieties. When a periosteal tumour forms on a long bone it presents itself as a hard, painless, smooth swelling without sinuses. It is probable that this type is due to direct inoculation of the organism into the periosteum of the tibia.

Cranial maduromycosis has been described by Brendan Hickey (1956) in three cases. There was loss of vision, proptosis and headache. The infective organism was *Streptomyces somaliensis*. The X-ray appearances are characteristic; there is expansion of the bone, periosteal new bone formation, also of punctate areas of osteoporosis without sequestrum formation. The picture may be confused with that of a neoplasm.

Culture.—Cultures can be made, as in actinomycosis, both under aerobic and anaerobic conditions on glucose or glycerol-agar plates, in shake cultures

or in Löffler's serum, as well as in Krainsky's and Czapek's media. Media are as follows: glucose peptone (1 per cent. Difco bacto-peptone) agar, Krainsky medium (glucose 10 grm., asparagin 0.5 grm., bipotassium phosphate 1 grm., agar 15 grm., water 1 litre). Czapek's agar (sodium nitrate 2 grm., bipotassium phosphate 1 grm., magnesium sulphate 0.5 grm., potassium chloride 0.5 grm., ferrous sulphate 0.01 grm., glucose 30 grm., agar 20 grm. and water 1 litre). Some workers recommend keeping cultures in an atmosphere of CO_2 . The medium should be inoculated directly with colonies from the pus, but, owing to slow growth of the actinomyces, pure cultures are somewhat difficult to obtain, unless the pus is free from contamination with other organisms.

Pathology.—On cutting into a mycetomatous foot or hand the knife passes readily through the mass, exposing a section with an oily, greasy surface, in which the anatomical elements in many places are unrecognizable, being, as it were, fused together, forming a pale, greyish-yellow mass. The bones have in parts entirely disappeared; where their remains can still be made out, the cancellated structure is very friable, thinned, opened out, and infiltrated with oleaginous material. Of all the structures, the tendons and fasciæ seem to be the most resistant.

The most remarkable feature revealed by section is a network of sinuses and communicating cyst-like cavities of various dimensions, from a mere speck to a



Fig. 126.—Section of a Madura foot. (T. R. Lewis.)

cavity an inch or more in diameter (Fig. 126). Sinuses and cysts are occupied by a material unlike anything else in human morbid anatomy. In the black varieties this material consists of a black or dark-brown, firm, friable substance which, in many places, stuffs the sinuses and cysts; manifestly it is from this that the black particles in the discharge are derived. In the white varieties the sinuses and cysts are also more or less filled with a white or yellowish roe-like substance, evidently an aggregation of particles identical with those escaping in the corresponding discharge. In the very rare red variety the colour of the accretions is red or pink.

Under the microscope the mycotic elements can be readily recognized in the concretions. In microscopic sections of the tissues, evidences of extensive degenerative changes, the result of a chronic inflammatory process, can be made out. There are differences in the pathology of different types of mycetoma.

Black mycetoma shows a marked tendency to spread along tissue planes and through fibrous tissue in the foot where numerous fibrous septa pass between the muscles and tendons. In the earlier stages of this deeper growth it may be possible to remove the tumour and it will be found enclosed in a capsule of fibrous tissue and may be dissected out.

Muscle tissue is resistant to invasion. A black mycetoma in a sheet of muscle on the back or buttock will grow for years without penetrating the muscle fibres. Nerves and tendons are also resistant.

Neurological complications and trophic changes are conspicuously absent in mycetoma. Yellow mycetoma caused by *S. somaliensis* shows an insidious growth. The edges blend imperceptibly with surrounding tissues. From the first these tumours infiltrate the underlying muscles. Yellow mycetoma is harder than the black. The fibrous stroma is more compact and in it the yellow grains may be embedded. Red mycetoma due to *S. pelletieri* is similar in gross pathology to the yellow. The sinuses are more numerous and active.

Treatment.—The only effective treatment is amputation, well above the seat of the disease; for the long bones may be implicated, as well as the small, and unless the entire disease be removed, it will recur in the stump. Complete removal is not followed by relapse. If a toe, or a small portion of the foot or hand, is alone involved, this may be excised. Potassium iodide in large doses has been found beneficial in certain forms.

Buchanan recommended surgical removal of as much diseased tissue as can be conveniently reached. Then tincture of iodine should be injected into any suspicious area remaining, in the hope that the surviving elements will be killed; thereafter 1–2 ml. of tincture of iodine should be injected every ten days for at least two months. At first, the local reaction is not severe, but later it becomes so. Probably a less irritating solution, such as Lugol's, would be better.

It has been shown that a number of fungi are inhibited by antibiotics.

Abbott has experimented with *M. mycetoni* and found it was unaffected with chloramphenicol, oxytetracycline, carbomycin and polymyxin B. On the other hand *S. somaliensis* is markedly sensitive to all these antibiotics, except polymyxin B, and is inhibited by carbomycin.

A number of cases of this infection have been given long courses of oxytetracycline and carbomycin and showed a good response with closing of sinuses and diminution of the tumour. One case was followed for two years and a recurrent sinus was healed.

Black mycetomas are much more difficult to treat. They are quite unaffected by antibiotics. In view of the demonstration in recent years of the value of the aromatic diamines in blastomycosis it was found that diaminodiphenylamine dihydrochloride at pH 7.0 inhibited four different strains at a concentration of less than 8 μ gm. per ml.

The practical results have been disappointing. No improvement was seen in nine cases of black mycetoma in which injections of 25–56 mgm. of *Stilbamidine* dissolved in 2 ml. of water were given into the femoral artery, twice weekly for ten injections.

Ochoa (1955) has shown that Dapsone (D.D.S.) is effective in nocardiasis caused by *Novardia brasiliensis* and should be given as *Novex* (22 "dihydroxy 55" *diechlorodiphenyl sulphide*) in extended trials preliminary to surgical exploration (Cockshott, 1957).

Chromoblastomycosis. "Mossy foot" (Fig. 127).—The disease was first recognized as a mycosis by Pedroso in Brazil (1911) who termed it "blastomycose negra." In 1915, Medlar isolated the causative fungus and named it *Phialophora verrucosa*. The fungus isolated from South American cases was named *Hormodendrum pedrosoi* Brumpt, and this proves to be the most common and widely distributed species, while *P. verrucosa* has not been found in hot countries.



Fig. 127.—Chromoblastomycosis of feet in a European.
(Dr. L. A. León, Quito, Ecuador.)

A third species *H. compactum* was discovered by Carrion in Porto Rico in 1935, but it appears to be rare. In 1943 a *Cladosporium* type was isolated in South Africa and Venezuela and later was recognized as the predominant form in Queensland. These were studied by Trejos (1954) in Costa Rica, and named by him *C. carrionii* n. sp.

The common species are acknowledged to be *P. pedrosoi* and *C. carrionii*. It is now accepted that the three species should be in the genus *Phialophora*—i.e., *P. verrucosa*, *P. pedrosoi*, *P. compactum* and that *C. carrionii* should remain separate.

The first three named species have spores and produce a hormodendrum-like sporiferous apparatus, and sometimes spores borne on a flask-shaped cell (phialide) with a cup-shaped extremity. Others are known as the *Acrotheca* form.

It is suspected that *Phialophora* are saprophytes in soil or timber, but as yet there is no sure proof. One instance has been recorded of *P. verrucosa* vegetating on commercial wood pulp in Canada. These fungi develop greyish or olive green velutine colonies, which become black and glabrous with age. They cause a papillomatous condition of the legs and feet first described by W. Thomas

in the Amazon Valley, Brazil, but now reported from Honduras, North, East and South Africa, South America, Porto Rico, Southern United States, Dutch East Indies, Japan, South Russia, Rhodesia and Queensland.

The foot and ankles—usually of males engaged in agriculture—are covered with warty outgrowths resembling barnacles, which are vascular and sometimes painful, a process which may take 15 years. They are usually papillomatous,



Fig. 128.—Lymphostatic verrucosis, from Ecuador.
(*Dr. L. A. León, Quilo.*)

but occasionally pedunculated. The sole of the foot usually escapes. This type occurs mainly in rural labourers exposed to trauma and contamination, but in Venezuela they are found on the upper extremities, and in Queensland on the head and upper part of the trunk, because the lower extremities are well protected. The type of lesion on the upper extremities tend to be flat, less papillomatous and less oedematous than those on the legs. These lesions may heal at the centre while spreading marginally, which, by coalescence, may form polycyclic outlines, but spontaneous cure does not occur. Cases of 20 years' duration are not uncommon and cases of double that length have been recorded. In general the prognosis is the same as in mycetoma. It is claimed that the disease can be inoculated into the nose of rabbits, producing a verrucoid mass.

The diagnosis is established by demonstration in sections of a tuberculoid type of reaction with rounded brown bodies resembling yeast cells, which multiply by splitting, not by budding. Mossy foot has to be distinguished from "lymphostatic verrucosis" described by Loewenthal and Manuwa (1935) from Uganda, Nigeria and Ecuador. This is a papillomatous condition of the soles of the feet, resembling mussels. The essential pathology is due to lymph stasis, oedema and hyperkeratosis (Fig. 128).

Treatment must be radical. Potassium iodide may be given as an adjuvant to surgical excision. Antibiotics are used to deal with secondary infection and to allay the putrid odour. Surgical excision is employed with subsequent skin grafting. Electro-coagulation is also used, but must be sufficient to destroy the fibrogranulomatous infiltration in the deeper parts of the dermis. If insufficient, there is danger of rapid extension through the lymphatics and development of *subcutaneous* chromoblastic nodules.

Verrucous mycosis.—Lie-Kian-Joe and colleagues (1957) have described in Indonesia a chronic infection of the skin by a fungus—*Cercospora apii*—belonging to a large group of plant pathogens which cause leaf spot disease. The patient, a boy aged 12, had extensive verrucose nodules and confluent patches on his

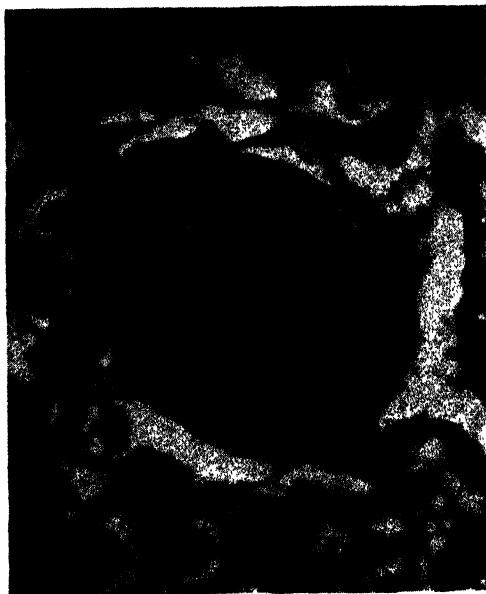


Fig. 129.—Sporangium of *Coccidioides immitis*. $\times 2,000$.
(W. St. C. Symmers.)

face with extension into the nasal cavities, and destruction of the turbinates and septum. The disease began in early infancy. On histological examination of biopsy specimens the brown, cephalate hyphae are visible. The fungus is easily cultivated from biopsy specimens as well as from nasal ulcerations. Experimental infection of tomato plants gave rise to "leaf spot disease."

Coccidioidomycosis—Posadas' disease—is probably the most infectious of systemic mycoses and the majority of individuals who live in the endemic areas acquire the infection.

The organism *Coccidioides immitis* appears as a non-budding, spherical thick-walled structure, 20–80 μ in diameter, which is filled with numerous endospores (2–5 μ). In cultures the fungus reproduces by these endospores which are freed by rupture of the cell walls (Fig. 129). The colonies are flat and greyish, with aerial hyphae which are septate and branching with spherical arthrospores. The disease occurs in South-West United States, in California, also in Texas, Arizona

Utah and New Mexico. A great area is in the Chaco regions of Argentina, Bolivia and Paraguay, the Comagayuvá Valley in Honduras and Nicaragua. The disease is endemic in arid zones from 40° lat. N. to 40° lat. S., where the climate is tropical or subtropical. The reports of sporadic cases in Italy and Egypt do not prove the existence of local endemic foci. Laboratory infections from cultures are very liable to occur. It may result in (1) primary coccidioidomycosis, a benign, self-limited respiratory disease; (2) progressive, a chronic, malignant, disseminated disease, involving cutaneous, subcutaneous, visceral and osseous tissues.

The greatest endemic focus is the San Joaquin Valley, where some six thousand cases in U.S. Army were diagnosed during the recent war, and skin tests have shown that 75 to 97 per cent. of children react positively to coccidioidin. Man acquires infection from an extraneous source, but it is found naturally in cattle, sheep and dogs. Possibly, rodents form a reservoir of infection. The arthrospores of *C. immitis* are produced in great quantity by the fungus vegetating in the soil when they are carried by the dust and wind over great distances, causing infection of man and animals at great distances from the original focus. In this, burrowing desert rodents may play a part.

In the primary pulmonary form, "Valley or Desert Fever," the organisms are inhaled with dust. Many are subclinical. There is a pneumonic type of infiltration, accompanied by skin lesions resembling erythema multiforme or erythema nodosum, with pronounced eosinophilia. In 80 per cent. changes in the lungs are demonstrated by X-rays as soft, fuzzy thickenings. Nodular lesions in the lung parenchyma measure 2-3 cm. in diameter.

The skin lesions which have been described may be determined by local trauma, but are almost certainly primary pulmonary in origin. The lesions ulcerate, exuding pus in which the organisms can be found (Fig. 130). After a few weeks the nodules become papillomatous. The scrofulodermic type involves the superficial cervical glands. In progressive coccidioidomycosis it occurs in 0.2 per cent. of cases of primary infection and develops into fatal form (Fig. 131). The symptoms and signs resemble chronic tuberculosis. Meningitis is found at autopsy in 25 per cent.

With regard to individual susceptibility there is no evidence of sex or racial predisposition, but there is a very marked difference in the prospect of progressive and disseminated disease. About 1 : 400 of all adult white males infected develop the granulomatous stage or about 1 : 100 of those in whom the primary disease is manifest clinically. In white females dissemination rates are one-fifth of those in white males. In male negroes the dissemination rate is 10 to 14 times greater than in whites. All coloured people and those of mixed blood are more



Fig. 130.—Cutaneous coccidioidomycosis (Wernicke or Posada's disease).
(Dr. L. A. León, Quito.)

susceptible. The mortality rate in the primary disease is very low, but in the granulomatous stage it is about 50 per cent.

Diagnosis.—In both forms of the disease, disseminated or granulomatous, diagnosis may be made by microscopy of pus or tissues or by culture.

In primary pulmonary forms these methods are not applicable and the diagnosis has to be based on the specific intradermal reaction to *coccidioidin*, as shown by

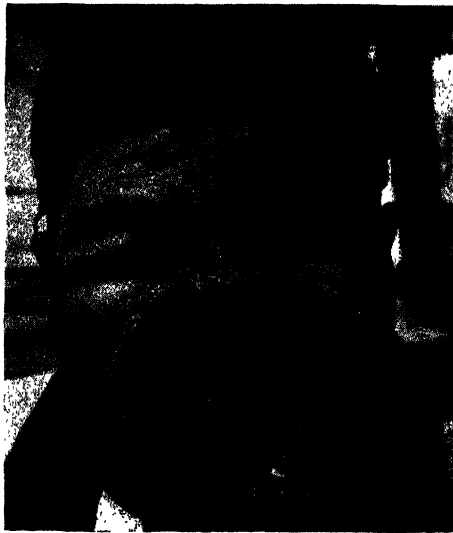


Fig. 131.—Coccidioidomycosis of face, Ecuador. (Dr. L. A. León.)

serial skin tests, and also by the demonstration of serum antibodies to coccidioidin antigens. Precipitins are often demonstrable in the early acute stages and complement-fixation antibodies in the progressive types. The test is also used in prognosis, when a rising titre of complement-fixing antibody indicates an extension of the disease. Radiography of the chest is important, especially in the primary stage and even in subclinical cases where remarkable pictures of pulmonary involvement may be revealed, quite out of proportion to the relatively mild symptomatology. Serial X-rays are a valuable guide to diagnosis and progress.

Treatment has, up to date, been mostly symptomatic. However, Gordon, Smith and Vedin (1955) have tested Nystatin (*Mycostatin*), an antibiotic, originally named *fungicidin*, which is fungistatic to cultures of *Coccidioides* in concentrations of 56–75 μ mgm. per ml. In disseminated coccidioidomycosis Hunter and Morgan (1959) have used an antibiotic—Amphotericin B, derived from species of streptomyces in soil from Orinoco river basin. It has antifungal properties for a wide variety of organisms. The infusion in concentration of 1 mgm. per kgm. daily, with a maximum individual dose of 50 mgm., is given intravenously. It is a water-soluble salt and is dissolved in 5 per cent. dextrooses.

North American Blastomycosis or Gilchrist's Disease.—*Blastomyces dermatitidis* appears in the tissues as a round, budding, yeast-like fungus and

produces aerial hyphae on Sabouraud's medium, which an isolated case in S. America and one each in France and England have been attributed to infection from fomites. Nearly all cases reported are in U.S.A., with a few in Canada and England. Natural infection has been found in dogs. There are two main types—systemic and cutaneous. The former commences in the lungs from inhalation infection and resembles tuberculosis. The latter causes ulcers of gummatous type on face, neck, hands, arms and feet. Bone infections occur in 60 per cent. and lesions of the C.N.S. in 30 per cent. It is recognized that the cutaneous form is primarily of pulmonary origin. The primary cutaneous form can be



Fig. 132.—S. American blastomycosis. (Lacoz and Pupo, São Paulo.)

experimentally produced, or by laboratory accidents. It is an entirely different disease and heals spontaneously. The port of entry is undoubtedly always the lung. In X-rays the striking feature is enlargement of the mediastinal glands.

Diagnosis is made from biopsy which shows extraordinary hypertrophy of the epidermis and from abscesses which show yeast-like organisms with double contour, 8–15 μ in diameter.

There is also an intradermal test with injection of 0.1 ml. standardized heat-killed extract of *B. dermatitidis* known as "blastomycin." X-ray therapy is also useful, but dangerous if there is a co-existent underlying tuberculous focus.

Treatment recently introduced (Colsky) is by 2-hydroxystilbamidine, dissolved in dextrose solution 5 per cent., 225 mgm. in 250 ml., intravenously, by slow drip, 40–60 minutes to complete. Treatment may last 50 days. Unfortunately many cases relapse after apparent cure.

South American Blastomycosis—Lutz—Splendore—de Almeida's Disease (*Paraccoccidioides brasiliensis*) is confined to S. America—São Paulo, the Amazon, Costa Rica and Panama. There is usually enlargement of lymphatic glands. (1) The cutaneous form is characterized by cutaneous and mucosal lesions, particularly in the region of the mouth, nose or vocal cords (Fig. 132). (2) The lymphatic type. (3) The visceral form with lesions in liver, spleen, etc. (4) The keleoid type (Jorge Lobo's Blastomycosis). (5) Central nervous type. Fifteen cases are reported. The C.S.F. is under pressure with high protein content and positive Pandy test due to granulomatous basic meningitis with large number of giant cells containing spherules of *P. brasiliensis*.

Diagnosis. Besides the recognition of the fungus, complement-fixation tests have been perfected. In culture both *B. dermatitidis* and *P. brasiliensis*, when incubated at 37° C. on a favourable medium, vegetate in yeast-like forms resembling those seen in parasitic life. At lower temperatures they vegetate in mycelial forms, closely resembling those of *Histoplasma capsulatum*. The characteristic form of the fungus in the tissues is larger than *B. dermatitidis* and shows a corona of gemmules or larger buds arising from all parts of its surface. The parasite is intracellular, often found in giant cells. The mycelial form of *P. brasiliensis* is more compact and slow-growing. Conidia, like those of *B. dermatitidis* are often absent.

The epidemiology is obscure and the natural habitat of the fungus is not known, nor has it been found in lower animals. It is now considered, on analogy with Gilchrist's disease, histoplasmosis and coccidioidomycosis, that primary infection of the lungs is probable. In view of the severity of the lesions in the mouth, it is held by some that the primary site was due to the habit of chewing leaves which might harbour the fungus.

Treatment.—Stilbamidine injected intravenously is effective, but 2-hydroxylstilbamidine is more so. Sulphadiazine as suggested by Quiroga (1949) and de Barros (1950) is used in solid form to ensure slower absorption. The dosage, 1 gm. by mouth every six hours, with a blood level of 1·1 mgm. per 100 ml. suffices.

Combined sulphadiazine and sulphamerazine can be given in doses of 0·5 gm. each by mouth every 3–4 hours. In all cases chemotherapy must be supplemented by dietetic management and by specific vaccine therapy. The effects of sulphonamides is fungistatic, not fungicidal. The best results are obtained in cutaneous, mucous and pulmonary forms of the disease. Glandular types are more resistant.

Failures and relapses after apparent cure have been reported. It is curious to note that although N. and S. American types are similar in their pathology and the fungi are related, the treatments which have given good results in the former have proved useless in Lutz's disease and *vice versa*.

Sporotrichosis.—Sporotrichosis, caused by *Sporotrichum schencki* (Hektoen and Perkins, 1900; Matruchot, 1910) (also known as *Rhinocladium beurmanni*), is found in many parts of the world, usually occurring sporadically or in small groups of cases, particularly among florists, horticulturists and people who handle raw vegetable products as packing material or for soil dressing. The fungus was found on the primitive plant *Equisetum* by Gougerot in 1908 and there is strong circumstantial evidence indicating its occurrence on berberis, rose, poinsettia, sphagnum moss and salt marsh grass. Lutz and Splendore (1907) found the disease in wild rats in Brazil; Gougerot and Caraven (1908) in the dog in France and Carougeau (1909) in the horse and mule in Madagascar, which resembles epizootic lymphangitis. However, the disease in the lower animals does not constitute a reservoir of infection for man.

Infection is caused by the introduction of the fungus into the skin on a thorn

or leaf spine causing a wound, but probably more frequently by contamination of a pre-existing abrasion or cut with material carrying the fungus. Benham and Kesten have transmitted the human parasite to carnations in which it produces "bud rot."

From 1941 to 1944 a unique outbreak of sporotrichosis involving 2,825 cases occurred in two mine shafts on the Witwatersrand where conditions of temperature (79.0 to 82.5° F.) and humidity (96–100 per cent.) were very favourable for the vegetation of *S. schencki* on the sound but unpreserved mine timbers. The fungus may have been introduced into the mines by miners already suffering from the disease. The infection was associated with contamination of cutaneous abrasions which were common on the mine workers. Mackinnon (1948), in his epidemiological observations on the disease in Uruguay, found that the infection rate was related to seasonal conditions of temperature and rainfall comparable to the temperature and humidity recorded in the Transvaal mines.

Following infection of the skin the incubation period is of variable length; in the South African mines it was from 7 to 14 days but it is sometimes up to 30 days or longer, occasionally as long as six months. The primary lesion is a cutaneous gumma, firm, elastic, painless and movable on the deeper tissues, measuring, on the average, about 1.5–2.0 cm. when well developed. As the gumma enlarges, its centre becomes necrotic and breaks down, becoming fluctuant, and the surface becomes dull red or violaceous in colour, a shallow ulcer with a little sinus may form at the apex and become crusted, but eventually the sinus enlarges, the summit breaks down and the contents of mucoid pus, in which the fungus can be found by culture, are discharged, leaving an indolent ulcer with overhanging, violaceous walls and a non-sloughing, granulomatous base from which a sero-sanguinolent fluid exudes and forms a crust. When the infection occurs on an open wound, the appearance of the primary lesion will be modified accordingly.

From the primary lesion the infection extends along a superficial lymphatic vessel causing an ascending mycotic lymphangitis with development of secondary gummata along the course of the thickened vessel. These secondary gummata tend to break down and ulcerate, but, except from secondary bacterial infections, there is generally an absence of concomitant lymphadenopathy.

The clinical picture of lymphangitic sporotrichosis is characteristic and a justifiable basis for a tentative diagnosis, but the isolated primary lesion, if not overlooked, may not suggest this infection, unless the diagnosis is indicated by the presence of other cases. In the established disease, the lesions are polymorphic and five clinical types have been recognized. *Hæmatogenous* dissemination of the infection may take place with the formation of multiple cutaneous and subcutaneous nodules, not related to the distribution of lymphatic vessels, found chiefly on the trunk, arms, forearms and thighs. These lesions are not unlike the localized gummata but they are not so prone to necrosis and ulceration although these changes may take place after 1 or 2 months.

A striking feature of all forms of uncomplicated sporotrichosis is the absence of any marked effect on the general health.

Involvement of bones may occur through direct extension from superficial lesions or as a result of hæmatogenous dissemination. Ocular sporotrichosis affecting the coverings and external parts or the interior of the globe is a rare condition.

Pulmonary sporotrichosis is very rare and probably always secondary to the superficial disease.

Diagnosis rests on the isolation of *S. schencki* in culture from the morbid material. It has also been found in the blood. Microscopy of pus smears or tissue sections rarely reveals the parasite although at a very early stage of the lesion, and in

experimental infections in animals (rats) the cigar-shaped, yeast-like forms of the fungus may be found, particularly in Gram-stained preparations. In the South African outbreak, where it was possible to make a very early clinical diagnosis and examine the young lesion microscopically, the parasite was often identified in its "asteroid" form, consisting of a large central yeast-like spherical body surrounded by a corona of long, hyaline eosinophil rays (the *Sporotrichum asteroides* of Splendore, 1909).

Diagnosis by culture is made by sowing material from a gumma (preferably an intact lesion) on glucose agar slants or Sabouraud's medium and incubating at room temperature—after 5–12 days at 24° C. the young colonies, of characteristic appearance, will be found.

The fungus is identified on its microscopic morphology, developed in microculture, but, although the microscopic features are very characteristic, it is advisable to refer cultures to a competent mycologist for diagnosis.

Treatment.—Potassium iodide is a specific in this disease, commencing with 10–15 grains (or 10–15 drops of a saturated solution) by mouth, in a few ounces of milk or water t.i.d. after food, and increasing by about 5 grains per dose per day until a maximum of 45–50 grains per dose is reached. This dosage should be maintained until clinical cure is achieved, and continued in a diminishing scale for a further 4 weeks to insure against recurrence. In the simple cases, treatment takes about 6 to 8 weeks, but the response will depend on the state of the disease and on the individual patient.

The more severe forms of the disease have been described by DeBeurmann, Gougerot, Matruchot and others in France from 1903–1912, where the disease was apparently common. It is now almost unknown in France.

Hemisorporosis (*Hemispora stellata*) is reported from Italy. It consists of granulomata resembling syphilis or tuberculosis and often attacking the bones.

Cryptococcosis (Torulosis, European blastomycosis) is a mycosis caused by the yeast fungus *Cryptococcus neoformans* (Sanfelice, 1895, Vuillemin, 1901 (with many synonyms, the most important of which is *Torula histolytica*), Stoddard and Cutler, 1916), which has a marked predilection for the central nervous system.

Two fatal cases were reported in London by Symmers in 1953.

Cryptococcosis is widely distributed in the world, but in man it is essentially a sporadic disease. The greatest number of cases has been reported in the United States, but the highest ratio in proportion to the population, in Australia. The causative fungus, *C. neoformans*, has been isolated from the soil and from the nests and accumulated droppings of the wild pigeon (*Columba livia*) which provide a favourable medium for the growth of the fungus (Emmons, 1951, 1955). The first recorded isolation of the fungus was by Sanfelice in 1894 who found it on decomposing fruit. It was found in milk in London by Klein in 1901 and in Glasgow by Carter and Young in 1950.

Cryptococcosis, as a naturally acquired disease of the lower animals has been described in the horse, rat, mouse, dog, cat, tiger, cheetah, marmoset monkey and the cow. Extensive outbreaks of cryptococcal mastitis have been reported in dairy herds in the United States (Pounden *et al.* 1952); the infection was transmitted through the suction cups of milking machines and the disease was generally confined to the udder. Nevertheless, there is no evidence that the disease in the lower animals is a source of direct infection of man.

The weight of circumstantial evidence points to infection of man by inhalation or aspiration of the fungal cells, with the primary lesion developing in the lung. Proof of this mode of infection has not been obtained in the individual case, and the possibility of infection, in some patients, through the alimentary canal or the skin must be admitted.

Cryptococcosis is a sporadic disease in man and there is no doubt that individual susceptibility plays a part in determining infection. Important predisposing factors are pre-existing Hodgkin's disease, lymphosarcoma, leukaemia and other malignant diseases of the reticulo-endothelial system, but it is probable that antibiotic therapy does not aid this infection as it undoubtedly does moniliasis.

In parasitic life, *C. neoformans* is seen as a thick-walled, spherical cell, surrounded by a wide capsular structure of mucoid character which is less refractile than the cell wall. Mounted in a suspension of China ink or nigrosin, the cell is seen to measure 5–15 μ in diameter and occasionally up to 20–30 μ , and the entire parasite, with its capsule, 15–45 μ in diameter. The young cryptococci are easily stained by Gram's method, but the best differentiating stain is mucicarmine with hæmatoxylin, which colours the cell wall an intense red and the contents and capsule a faint pink.

The parasite multiplies by gemmation, does not produce endospores, or mycelium, and can be cultivated in glucose broth or on Sabouraud's medium. The colonies are honey-coloured and semi-fluid.

The primary disease in the lung may extend locally but it frequently undergoes partial or complete resolution; in the meantime, the cryptococci may have been carried in the blood stream to other organs and tissues, causing secondary foci, particularly in the central nervous system where cryptococcosis of the cerebral and sometimes the spinal meninges, or meningo-encephalitis, results. Other organs not uncommonly affected are the kidney, spleen, adrenal, skin and subcutaneous tissues, lymph nodes and bones. Although disease of the central nervous system has been reported most commonly and about twice as frequently as that of the lung, primary infection of the central nervous system is probably extremely rare, and a minute examination of the lungs in fatal cases of intracranial cryptococcosis, generally reveals minute healed lesions likely to be overlooked in a more casual examination.

The lesions of cryptococcosis in the brain tend to be of a gelatinous or myxoid character from the presence of great numbers of thickly capsulated cryptococci and the almost total absence of any inflammatory reaction. Cryptococci reach the brain through the blood stream, or from the subarachnoid space along the perivascular lymph channels on the cortical branches of the pial vessels. The cryptococci, multiplying in these channels, generally within endothelial or multinucleate cells, but later extracellularly, form a gelatinous nodule around the little vessel. These nodules, usually multiple, increase in size and coalesce, causing pressure atrophy of the surrounding and intervening brain tissue. This tissue destruction without inflammatory reaction led to the erroneous assumption that it was due to a histolytic enzyme of the fungus, and to the name *Torula histolytica*, proposed by Stoddart and Cutler, 1916.

In other tissues the character of the lesion is influenced by the ready availability of reticulo-endothelial cells and the stimulation of a granulomatous infiltration, so that it may vary from the almost purely myxomatous, through the myxo-granulomatous to the almost granulomatous character. The cutaneous form—"Busse-Buschke's disease" (sometimes called "European blastomycosis") may follow systemic infection.

The infection, *per se*, has little tendency to cause fever or constitutional symptoms, and the symptomatology therefore depends upon the organ or organs affected. *Lingua nigra* or black tongue, which is characterized by hypertrophy of the filiform papillae and hyperpigmentation, is due to *Cryptococcus linguae pilosæ*, and is curable with nicotinic acid and can be cultured on maltose agar.

Diagnosis.—There is little in the clinical picture to indicate the nature of the infection and, up to recent times, the diagnosis was almost invariably made

at autopsy. However, the absence of constitutional symptoms, in some cases, in the presence of marked focal symptoms and sometimes mental disturbance may arouse suspicion. In general, however, the discovery of *C. neoformans* in cerebrospinal fluid, pus or sputum is the first indication of the true nature of the infection. In wet mounts of these materials in China ink or nigrosin, the cryptococcus, with its wide capsule, stands out sharply. In biopsy or necropsy material in sections, the microscopic picture of the mucoid lesion is sufficient for diagnosis. In the fresh, unfixed tissue, the cyst-like lesions are seen to be filled with the thickly-capsulated cryptococci and in fixed and paraffin embedded tissues, from the shrinkage and disappearance of the capsular material the cryptococci appear to be lying free in a cavity or supported by a meshwork of mucinous threads. In the more granulomatous lesions the cryptococci may be very scanty and difficult to find, and in such cases, staining by mucicarmine or by the periodic acid-Schiff technique, will generally lead to their discovery.

For wet mounts of the centrifuged deposit from cerebrospinal fluid it is advisable to wash the deposit gently in saline before mounting in China ink as the albuminous material may cause clumping of the ink particles. By cerebrospinal puncture the protein content and globulins are raised as in other forms of meningitis. The sugar content is lowered and chlorides reduced.

Serological tests are of no value in diagnosis, but in some cases of extensive disease there is sufficient capsular antigen in the cerebrospinal fluid or the peripheral blood to give a specific precipitin reaction with a hyperimmune test serum.

This circulating antigen may, in some cases, account for the general absence of specific dermal hypersensitivity.

Diagnosis by culture presents little difficulty, and if the morbid material has been collected from an uncontaminated source, such as the C.S.F., blood, or a clean biopsy, the sowing may be made on a simple glucose agar medium. If, however, there is a possibility of contamination by bacteria, as in the case of sputum or pus from an open sinus, the glucose agar medium should be enriched with penicillin 20 units and streptomycin 40 units per ml.

Cultures are incubated at 37° C. to distinguish *C. neoformans* from non-pathogenic cryptococci which cannot vegetate at this temperature. Control cultures may be put up at about 24° C. to detect the nonpathogens. After 48 hours incubation at 37° C. the initial growth is usually visible as little whitish, rather dry colonies which become wrinkled as they grow. At a later stage, or in subculture, the culture may develop its characteristic mucoid character, becoming fluid as it develops and collecting in a pool at the bottom of the s'ant. Older cultures are honey colour to brownish with greyish mucoid streaks.

Microscopically, the cells in culture measure, on an average, 4-6 μ in diameter, spherical or ovoidal and usually show a capsular structure in nigrosin or China ink mounts.

Identification of C. neoformans in culture.—The growth at 37° C. is an important character. The species is not known to ferment any carbohydrate with liberation of gas. Production of acid in these media varies with the strain. Cultures on a chemically defined synthetic agar medium containing glucose, can be shown to have synthesized a starch-like substance, by flooding the plate with Lugol's iodine—this is an important character of the group.

Test of pathogenicity: with rare exceptions the species is virulent and pathogenic to the mouse when injected intracerebrally in a dose of 100,000 cells, and by subcutaneous, intraperitoneal and intravenous injection.

Treatment.—Chemotherapy has hitherto proved disappointing. The antibiotic cycloheximide, after some promising preliminary tests, has proved disappointing. Another antibiotic, nystatin, has proved hopeful *in vitro* and in some tests *in vivo* in mice, but its effect in cryptococcosis in man has not yet been

demonstrated. Rounse and Lerner (1958) report favourably on amphotericin, a new antibiotic given intravenously, 1 mgm. per kgm. body weight, up to total of 1 grm. over a period of 18 days. Martin and colleagues (1959) had some success with 100 mgm. dissolved in 500 ml. of 5 per cent. dextrose injected daily for six weeks.

The few successes in therapy must be credited to surgical procedures, in nearly all cases carried out on a wrong diagnosis or as a diagnostic measure. Isolated lesions of the lung have been removed by lobectomy but the operation may entail the risk of dissemination. The successful removal of a toruloma of the brain, mistaken for a tuberculoma, has been recorded, but the indication for this kind of treatment must be extremely rare.

In lesions in other parts, accessible to surgery, excision or amputation is sometimes justifiable.

Prognosis.—The prognosis depends, in part, on the system involved, but it is generally bad. Lesions in the lung, skin or lymph nodes may sometimes undergo spontaneous cure, but when the central nervous system is involved the outlook is immediately grave. In most cases, death occurs within 6 months of the onset of signs of intracranial disease, sometimes in a matter of days. On the other hand, rare cases have been reported of survival with extensive pulmonary and meningeal disease, in one case for nearly 16 years, with intermittent periods of fairly good health.

Histoplasmosis (*Histoplasma capsulatum* : *Cryptococcus capsulatus*).—Histoplasmosis (reticulo-endothelial cytomycosis), discovered by Darling in 1905–1906 when seeking for kala-azar in Panama, is a mycosis in which the cells of the reticulo-endothelial system are parasitized by the capsulated, yeast-like form of the fungus, often present in great numbers in the host cells.



Fig. 133.—*Histoplasma capsulatum* from a smear preparation from a cutaneous lesion. (Dr. Alvarez Crespo, Guyaquil.)



Fig. 134.—*Histoplasma capsulatum* in skin section. About $\times 2,000$.
(W. St. C. Symmers.)

The disease occurs in a relatively benign and mainly pulmonary form which has a marked tendency to undergo spontaneous cure, and an uncommon, grave, disseminated form with a high mortality rate.

The disseminated disease, which was the type seen by Darling in the three necropsies in Panama, bears a clinical resemblance to tuberculosis, with granulomatous lesions in various organs and tissues, which tend to undergo suppuration, necrosis, caseation, calcification or fibrosis. The granuloma is formed mainly of histiocytes, with some multinucleate giant cells, in which great numbers of the yeast-like parasite may be seen, as oval capsulated cells measuring 3.0 to 3.25μ in diameter, in fixed specimens, and the capsule about 0.65μ in thickness. (Figs. 133–134).

Symptoms in the disseminated disease include fever, sweating, malaise, weakness, loss of weight and anæmia—the anæmia may be slight and of the hypochromic type, but in some cases it is marked and severe through involvement of the blood-forming organs and from frequent intestinal hæmorrhages. In infants, the blood picture may resemble that of “aleukæmic leukæmia.” Splenomegaly, hepatomegaly, lymphadenopathy and sometimes papular and ulcerative lesions of the skin and mucous membranes are characteristic, and other symptoms may be referred to particular organs such as the lungs and adrenals.

Histoplasmosis may occur at any age, from the infant a few weeks old to the aged. Statistics of the grave form of the disease show that men are affected much more frequently than women, the ratio being about $7 : 1$.

As an occupational risk, it can be regarded as a disease of farmers and others engaged in rural occupations. Schwartz recognizes four main forms of pulmonary histoplasmosis, each with an active and inactive stage, i.e., a benign primary infection resembling a primary T.B., a chronic reinfection, a mediastinal form resembling lymphosis, a diffuse interstitial pneumonic form resembling miliary tuberculosis. Recent tests in Rio by Carvalho on 3,653 people, as the result of severe and fatal infections, showed that 16.4 per cent. reacted to *histoplasmin* and 89 per cent. to *tuberculin*.

The organism grows on Sabouraud's medium at room temperature and on blood agar at 37° C. On the former it produces white, cottony, aerial mycelium, later becoming brown; on the former medium too, there are dull white colonies consisting of yeast-like cells with fragments of mycelium. Reference should be made to the mycelial forms. It should be stated that a yeast-like phase of the fungus, resembling the parasitic form, can be obtained by sowing the mycelial form on blood agar and incubating at 37° C. Reversion to the mycelial phase occurs when cultures in the yeast phase are incubated at any temperature below about 34° C.

After Darling's discovery in 1905-1906, no other instance of the disease was reported until 1925 when a case was diagnosed in Minnesota, and in 1934, when DeMonbreun reported the first successful cultivation of the fungus, *Histoplasma capsulatum*, the disease was still considered to be very rare, but about ten years later, a number of investigators in the United States drew attention to the existence of a high incidence of residual pulmonary lesions, frequently calcified, in young people living in certain areas in the central-eastern part of the country. These lesions, brought to light in the campaign of mass radiography of the chest, were, in most cases, not attributable to tuberculous infection, and extensive were, in most cases, not attributable to tuberculous infection. Extensive studies, with the histoplasmin skin sensitivity test and the tuberculin test, indicated was obtained by serological tests in the more recent cases, and in some patients by cultivation of *H. capsulatum* from sputum or stomach washings.

The result of these investigations revealed the existence of an enormous area in the Mississippi-Missouri-Ohio river valleys, where histoplasmosis is endemic, but, because of its relatively mild and frequently subclinical form, it had not been recognized previously.

H. capsulatum has been isolated from the soil on many occasions and there is no doubt that it has a natural habitat as a soil saprophyte. Its occurrence in the soil has almost invariably been associated with contamination by the dejecta of fowls or pigeons. Neglected chicken coops, especially disused coops, dove cotes and places infested by bats have proved fruitful sources of the fungus, which vegetates on the excreta of these animals, but no instance of infection of bird or bat by *H. capsulatum* has yet been discovered. Numerous cases of groups of persons infected through cleaning old chicken coops, pigeon lofts, or disused silos have been reported, and others have been infected during a visit to cellars, bat-infested caves, etc., and in such cases it has been possible to record the events from the moment of exposure to infection. From these reports and from numerous laboratory infections there is no doubt that the fungal spores gain entry through the lungs by inhalation. The incubation period and severity of the resulting disease will depend, apart from other factors, on the intensity and duration of the exposure at the point source of infection.

Notable outbreaks of histoplasmosis as "cave disease" have been reported in Venezuela (Campins *et al.* 1955), the Transvaal (Murray *et al.* 1957) and Rhodesia (Dean, 1957), Tanganyika (C. Manson-Bahr, 1959), in groups of people visiting bat-infested caves or disused mine shafts. In the Transvaal outbreaks, members of a Speleological Association exposed for the first time in caves known to be sources of the infection, were the subjects of a careful study of the primary

pulmonary infection. The incubation period was from 14 to 9 days, according to the duration and intensity of the exposure. The symptoms were those of a moderately severe pneumonitis with lassitude, headache, fever, pains in limbs and joints, backache, coryza and non-productive cough. Persistent dyspnoea was often encountered and in severe cases there were rigors. Radiography of the chest showed widespread miliary nodulation, or patchy dullness suggesting virus pneumonia, or localized groups of pea-size nodules and a general increase in the broncho-vascular shadows.

The acute stage of the disease generally lasted from 1-3 weeks and was followed by apparently complete recovery. Towards the end of the acute stage, complement-fixation antibodies for *Histoplasma* antigen were demonstrable in the blood of some of the patients, and all developed specific cutaneous sensitivity to histoplasmin in from 4 to 8 weeks of the onset of symptoms, and this sensitivity generally persisted.

This brief outline of the clinical features in a moderately severe attack of primary pulmonary histoplasmosis, contracted in bat-infested caves, is also of infections from chicken coops and pigeon lofts in the United States, and of the more severe laboratory infections. In general, however, the relatively light infections from undetermined sources, particularly in urban areas, result in a much milder disease which is frequently subclinical.

In contrast to the ease with which the fungus has been isolated in culture from animal sources of infection in the United States and from some patients with the primary pulmonary disease, all attempts to isolate the fungus from patients or directly from the bat guano in caves in the Transvaal were unsuccessful. Eventually, proof of the source of infection in the Transvaal case was obtained by exposing various animals in cages in the suspected caves, and after a few weeks, isolating the fungus from the tissues of the infected animals. In one instance the fungus was isolated, by animal inoculation, from washings of a respirator filter used by one of the cave explorers.

In the United States, *H. capsulatum* has been found causing natural infection in the dog, cat, brown rat, roof rat, mouse, spotted skunk and opossum, but these animal infections do not play any known rôle in human infection, nevertheless they contribute data on the distribution of the infection.

The disease is not transmitted from man to man or from animal to man, but possibly to a limited extent from animal to animal living in close contact.

The diagnosis, in the disseminated form of the disease, depends upon the identification of the fungus microscopically in the lesions and, more conclusively, on its isolation in culture from the morbid material. In the primary disease, microscopical diagnosis is rarely possible and diagnosis by culture would depend on sputum or stomach washings from active lesions in the lung. The Transvaal cases, which were under observation from the time of infection, illustrate the difficulty in making a direct mycological diagnosis in the transient pulmonary disease. In such cases the diagnosis is generally based on the result of serial serological tests, precipitin tests at the earliest stages and complement fixation tests at a later, but still active, stage.

Precipitins are transient and may not be present, complement-fixing antibody may be found in moderately severe and severe cases about the end of the acute stage, but sometimes earlier. Salvin has prepared from the yeast forms an antigen for complement-fixation known as "Y.P." The antibody titre tends to rise fairly sharply and to fall almost as steeply, although a low titre may persist for some time. Serial histoplasmin skin sensitivity tests, which show a change from histoplasmin-negative to histoplasmin-positive during the illness, provide diagnostic evidence in the absence of other data.

The history of possible exposure and the radiological picture of the lungs showing a striking pattern, not specific but often out of proportion to the mildness

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of the symptoms, should be taken into account. Radiography reveals enlarged hilar glands with peribronchial thickening and sometimes nodular lesions. The diagnosis can be made by biopsy and organisms are best seen in smears. They have to be distinguished from *Leishmania donovani* and appear as small, oval bodies or mononuclear cells. They have also been demonstrated in sternal puncture.

Treatment.—Chemotherapy has hitherto proved disappointing. Ethyl vanillate, a byproduct of the sulphite pulp manufacturing process, was used with apparent success in some of a group of 12 children with disseminated histoplasmosis; 5 recovered. However, further trials with this drug on adults have not confirmed its value. Radiotherapy has given, at best, very unequivocal results, but surgery, when it results in extirpation of an entire focus of the disease, has been successful—excision of cutaneous nodules and lobectomy for solitary pulmonary lesions. A new antibiotic from young tomato plants—*Tomatin* (Squibb) may prove effective. It has given good results in mice.

Prognosis, in the benign form is excellent, but in the disseminated disease the mortality rate is high.

Geographical Distribution.—Histoplasmosis is chiefly a disease of the New World and particularly the United States. Sporadic cases and small groups of infections have been identified in the Old World—Australia, Austria, Belgium, Bulgaria, G. Britain, France, Germany, Holland, Spain, Turkey, India, Indonesia, Philippines, South Africa and Portugal. Some, at least, of these cases were not autochthonous infections. Duncan had reported on five cases of authentic histoplasmosis in England since 1941. Surveys by the *histoplasmin* test have given trustworthy evidence where the results have been entirely negative and a safe inference is that the infection was not present in the area.

Positive results compiled and analyzed by Mochi and Edwards for W.H.O. (1952) showed significant reactor rates in areas where, sometimes, the existence of the disease had not been suspected. In a later report, Edwards *et al.* (1956), it was pointed out that the minimum positive reaction generally accepted was an area of induration 5 mm. in diameter, read, 24, 48 or 72 hours after the intradermal injection. They found, however, that a delayed reaction of that size could be given to an injection of the buffer fluid used in preparing the histoplasmin for injection. Data based merely on the proportion of positive results, without reference to the intensity of the reaction, may therefore prove misleading in epidemiological surveys.

The *histoplasmin* used for either diagnostic (including serological), or epidemiological, tests is a standardized preparation of a filtered culture autolysate of the mycelial form of *H. capsulatum* grown for several weeks in a chemically defined synthetic liquid medium, at room temperature. The method of preparation is the same as that used for production of coccidioidin, blastomycin and other antigens.

In 1943, Duncan identified a form of histoplasmosis in a patient from Ghana, which was distinguished from the classical disease of Darling by the large size of the intracellular parasite, which measures 3 to 4 times the diameter of *H. capsulatum*. In culture, this fungus, which was named *Histoplasma duboisii* by Vanbreuseghem in 1952, from another isolate, can be distinguished from *H. capsulatum* by its greater tendency to develop large, thick-walled, resistant cells in yeast phase cultures exposed to a relatively adverse environment, but particularly by the reproduction of the large parasitic form and the characteristic histopathology of the African disease, in mice or rats experimentally infected with the culture.

Hitherto, 21 cases of this variety, which appears to be peculiar to tropical Africa, have been reported from Ghana, Nigeria, Belgian Congo, French Sudan and Senegal, and a similar disease was identified in a group of monkeys from

French Guinea by Mariat and Segretain (1956). In several cases, the presenting features of the disease have been cutaneous ulcerations and subcutaneous abscesses, and in two patients with minor cutaneous lesions spontaneous cure has been reported, but in 6 instances the disease was systemic or generalized and fatal.

Drouhet (1957) considers the basis of the species *H. duboisii* to be inadequate and recommends that the name and the identity of the type be preserved as a sub-species or a stable variety of *Histoplasma capsulatum*.

Moniliasis.—The most widespread of the fungus diseases, assuming many forms, increased in incidence and importance since the introduction of antibiotic therapy, and of special interest in tropical medicine because of its intertriginous cutaneous form prevalent in warm climates and likely to be mistaken by the inexperienced for "Dhobie's itch."

Moniliasis (Candidiasis, thrush, etc.) is a mycosis affecting chiefly the mucous membranes and the skin. It is caused principally by *Candida albicans* (Robin) Berkhout, and occasionally by other species of *Candida*, notably *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii* and *C. krusei*.

The disease is found in all countries and the infection is almost invariably autogenous, *C. albicans* being a frequent commensal in the alimentary canal.

In particular circumstances, infection of the deeper organs and tissues may occur, but it is a fungus of low virulence.

C. albicans causes moniliasis in man, monkey, fowls, turkeys, pigeons, and possibly the cat, dog, goat and dingo, and it occurs as a commensal in the hedgehog, rabbit and rat, as well as in the animals mentioned above. It can survive in contaminated soil but it is not known to have a natural habitat in inanimate nature. The other species are mainly known to have a common saprophytic existence apart from the animal host.

The incidence of moniliasis has shown a marked increase since the introduction of antibiotic therapy and particularly the use of the wide-spectrum chlortetracycline, which, in various indirect ways, creates a predisposition to the infection.

Moniliasis, as oro-pharyngeal thrush, is a common disease of the new born and young children, and in the former group, especially premature and debilitated infants, it is an important cause of death. In women, especially when pregnant, vaginal moniliasis is not uncommon and it is a cause of napkin rash on infants. Infants suffering from oesophageal thrush tend to regurgitate their food and aspiration into the lungs may have fatal results in which infection of the organ by *C. albicans* plays a part. Oral and intestinal moniliasis have been found frequently, as shown by the Editor, as terminal infections of sprue in the tropics, and at one time it was thought to be the cause of the disease.

Intestinal moniliasis, like the oral form, has greatly increased and achieved a new importance since the commencement of the antibiotic era, and in connexion with this, muco-cutaneous lesions may be found at both ends of the alimentary canal—perianal and ano-genital moniliasis by direct extension, and at the other end, perlèche at the angles of the mouth.

A chronic, granulomatous form of thrush, manifested by infiltrated, leukoplakia-like lesions in the mouth with ulceration and often deforming scars, as well as chronic granulomatous lesions affecting the skin and nails, is not uncommon. It starts in infancy or early childhood and is associated with various deficiencies and debilitating conditions. It tends to persist into early adult life when death usually occurs from some intercurrent disease. Pulmonary moniliasis is a frequent terminal infection in pulmonary tuberculosis and is usually an extension from the mouth. From time to time attempts have been made to recognize pulmonary moniliasis as a primary disease, but the general opinion regards it as a secondary manifestation. Complete casts of monilial infection of the bronchial tree have been recorded.

Systemic moniliasis is rare, but instances of endocarditis caused by *C. parapsilosis*

silosis were reported by Pasternack (1942) and meningitis and other forms of intracranial moniliasis by Miale (1943), Morris *et al.* (1945), Halpert and Wilkins (1946) and Zimmermann *et al.* (1947).

A local or a generalized invasion of the alimentary mucosa, followed by a *Candida* septicæmia, is not rare as a terminal event in diabetics and others suffering from chronic cachexial conditions. In such invasions, however, the fungus is of low virulence.

Alimentary moniliasis, provoked by antibiotic therapy, may lead to systemic infection of various organs and, sometimes, embolism and infarction. However, the pathogenicity of these fungi in the deeper tissues is not great and, according to Mackinnon and Artagaveytia-Allende (1956), removal of the alimentary source of the infection by efficient treatment (Nystatin) will generally be followed by the spontaneous cure of the deep lesions.

Cutaneous Moniliasis.—This is of particular importance in warm climates where the humid state of the skin, especially in the intertriginous areas, greatly conduces to the disease. These cutaneous lesions generally resolve spontaneously with removal to a cool climate or with the onset of a cool season, but recur with return to warm, humid conditions.

The forms of cutaneous moniliasis are: Intertriginous, generalized, paronychia, onychia, peri-anal, ano-genital and perlèche.

The intertriginous form occurs in the inguinal, genito-crural, gluteal, peri-anal inframammary, axillary, interdigital of the hands and feet areas.

The genito-crural infection is manifested at first by little papules or vesicles, 1–2 mm. in diameter, isolated or in groups. The papule is slightly raised, of a dull red colour, with a scaling surface and is surrounded by a narrow inflammatory zone. These initial lesions increase in size and coalesce to form large, raised plaques and as these increase in size the central part becomes less scaly, is erythematous or violaceous in hue and still shows the crusts of dried vesicles and some excoriations. The marginal zone is active and covered with a thick layer of whitish sodden epithelium in which vesicles are common, and ends abruptly in a prominent, raised border surrounded by zone of inflammation. Satellite lesions are common and in consequence the border often presents a festooned outline.

Although the appearance may be slightly modified by the chafing of the opposed surfaces, the general character is very typical of moniliasis; the red or violaceous central area with crusts and excoriations and the heaped-up margin of sodden, whitish epithelium being quite distinctive, and unlike the picture of *tinea cruris*.

The interdigital type presents the same basic characters, modified by the situation. When the vesicles rupture, an erosion with ragged, undermined borders and a weeping base is left. On the foot, it may be mistaken for *tinea pedis*.

The generalized form occurs chiefly in infants and may be associated with oral thrush, or moniliasis of the napkin area. It spreads to the main flexures and eventually may involve the entire skin in an erythematous-squamous, vesicular and pustular eruption.

Higdon (1956), reporting on intertriginous moniliasis among United States Army personnel in Japan, pointed out that although the disease was uncommon among the native civilian population (who are often infected with *Tinea cruris*) and among American service women, it presented a problem in connexion with the male members of the service, of whom about 300 suffered more or less severely every summer season. The explanation of this peculiar distribution of the disease appears to be the warm, tightly-fitting, unventilated uniforms worn by the men, which induce a continual state of sweating and humidity of the skin in the groin and similar areas in the hot weather.

Treatment by the usual methods, including Castellani's fuchsin paint, wet compresses of 1 : 4,000 potassium permanganate and soothing applications followed by a paint of 0.1 to 0.5 per cent. methylrosaniline chloride (gentian violet) at bedtime, and asterol dihydrochloride causes only moderate benefit. A nystatin lotion or powder, however, gives immediate relief and eventual cure in a majority of cases. The nystatin lotion is prepared by suspending the antibiotic powder in 60 ml. of a basic lotion of talc 6 gm., zinc oxide 6 gm., glycerine 6 ml., "Bentomite magma" 12 ml., and water to 60 ml. to give a concentration of 35,000 units of nystatin per ml. The lotion is applied t.i.d. It does not keep and should therefore be dispensed in small quantities and stored in the cold.

A valuable additional measure which reduces the period of topical chemotherapy to about one-half, is to construct a wind tunnel on the patient in bed by placing a wire cage over his lower part, draping the sheets over this and setting an electric fan at his feet so that, with his legs apart, the genito-crural area is kept dry and cool by the air current.

Spontaneous relief occurred in all patients in the cool season, but recurrence followed in the next hot season. However, since the use of the treatment described, the infection rate in the hot season diminished markedly.

The antifungal antibiotic Nystatin is a specific in the treatment of all forms of moniliasis, and, although it is insoluble, it can be administered by the mouth for the treatment of some of the deeper forms of the infection, and it can be given in conjunction with broad spectrum antibiotics to counteract their effect in promoting attacks of moniliasis.

As moniliasis is a disease of the debilitated, supporting treatment should also be given and the vitamin B complex is particularly valuable.

Diagnosis is made by microscopy and by culture of the fungus. The former to diagnose the disease and the latter to identify the species of fungus.

Scrapings from mucosal or skin lesions, mounted in caustic potash solution or fixed and stained by Sahli's methylene blue or Gram's method, show the characteristic morphology of the fungus in the epithelial scales. A pseudomycelium formed by apical budding of the constituent cells, without separation of the daughter cells, so that a chain of elongated cells is formed, and subapically from the distal pole of each segment of the chain a cluster of yeast-like cells arises or elongated cells which form branches.

In culture, which is easily obtained on glucose agar, in glucose broth or in liquid potato extract, the morphology of the fungus is the same as in the lesion. They are mycelium-forming yeasts which do not form ascospores. In addition to pseudomycelium, a true, slender mycelium of long tubes with parallel walls, septate at long intervals, is also formed with blastospores arising characteristically from the distal poles of the segments of the main hypha and its branches. The development of large, thick-walled terminal chlamydospores is a distinguishing feature of the most important species, *Candida albicans*. Identification of species rests largely on minor features of the gross and microscopic morphology and on fermentation of certain carbohydrates with gas formation and the auxanographic tests of capacity to utilize certain compounds as sources of essential carbon and nitrogen. Pathogenicity tests on rabbits and mice also constitute an important means of identification of the outstandingly pathogenic species, *C. albicans*.

MUCORMYCOTIC GRANULOMA, due to *Basidiobolus ranarum*, a mould in the intestine of frogs and lizards which causes subcutaneous granulomata in man, and occasionally cerebral infection, was reported in two boys by Lie-Kian-Jo in Indonesia (1956) and in a Dutch girl from there in London by Symmers (1960).

Section V.—DISEASES OF THE CENTRAL NERVOUS SYSTEM

CHAPTER XXXVII

EPIDEMIC FORMS OF ENCEPHALITIS AND ANTERIOR POLIOMYELITIS

Under the heading of epidemic encephalitis a number of clinical entities have emerged which possess approximate symptom-complexes and somewhat similar pathological changes. With the exception of Von Economo's disease, these conditions occur chiefly in specific geographical areas.

(1) **Von Economo's disease** (Encephalitis lethargica, sleepy sickness, type A encephalitis).—This serious encephalitis has occurred in epidemic, less often, in spurious outbreaks. It was brought into prominence by Von Economo's report of the Vienna outbreak in 1917. In the following years cases were recognized in New York, and, subsequently, in other parts of the world. Though it is generally considered to be a virus infection, the agent has not yet been discovered. It occurs most commonly between the ages of 10 and 40 years. Males are more commonly affected than females in a proportion of 3:2.

The pathological lesions are common in basal ganglia, midbrain and pons. They consist of hyperæmia, small petechial hæmorrhages and perivascular cuffing. The incubation period is 2 days to 3 weeks: the onset abrupt and insidious. The temperature is 100–102° F. with stiff neck and back. Lethargic encephalitis is not a satisfactory description, because *lethargy* is not the commonest symptom. There is an increase of muscle tone, coarse tremors, weakness or paralysis of one or more extremities. The third phase—the chronic—may be deferred for years. Then there ensues increasing rigidity of muscles resulting in slowed associated movements and ends in the Parkinsonian syndrome.

(2) **St. Louis encephalitis** (American encephalitis).—This encephalitis is due to a filterable virus (Webster and Fite) which is allied to Japanese B, Murray Valley and W. Nile viruses (*see* p. 338). It occurs mostly in the Central and Western portions of the U.S.A., and it did so in the summer of 1932, in and about Paris, Illinois, where more than 1,000 cases were reported from St. Louis County alone with a case mortality of 20 per cent.

Ætiology.—The virus particles (discovered by Muckenfuss, Armstrong and McCordock in 1933), which are produced by inoculation of human brain into monkeys, measure 20–30 m μ . The virus has been cultured on the chorio-allantoic membrane of the chick embryo and is transmissible to monkeys in which it produces changes similar to those found in man.

Epidemiology.—St. Louis encephalitis occurs in the late summer and autumn months, principally in the Central and Western parts of the U.S.A. The implication is that it is spread by mosquitoes, especially *Culex tarsalis*. Chickens and other birds are probably reservoirs of the infection. The virus has been recovered from chicken mites.

Clinical picture.—The incubation period is about 4–21 days. The clinical manifestations vary, depending upon the severity of the infection. Moderate cases develop fever, headache, muscular pains and sore throats, followed by central nervous system phenomena. Severe cases have an acute onset with high

fever (102–105° F.), nausea, vomiting, dizziness and a moderately stiff neck. The deep reflexes are exaggerated. When paralysis occurs it is spastic in type. The cerebrospinal fluid is under increased pressure. It is clear to hazy in appearance with cell counts ranging from 50–500 cells.

(3) **Western equine encephalomyelitis** (or encephalitis).—This is a neurotropic virus disease of horses, mules and other lower animals and is transmitted to human beings.

Epizootics of this encephalitis in Army horses and mules have been known in U.S.A.

Meyer, Haring and Howith isolated the virus in 1931.

Ætiology.—Western equine encephalomyelitis is due to a filterable virus and distinct from that of the Eastern form. It is about 25 mμ in size and grows readily in tissue culture. Distinct, also, from St. Louis encephalitis it shows slight antigenic relationship with Russian Spring-Summer encephalitis (EEE virus) in complement-fixation tests. It is transmitted by *Culex tarsalis*. Syverton and Berry (1941) transmitted this disease to animals by experimentally-infected wood ticks, *Dermacentor andersoni*. Another virus (Turlock) has been isolated also from *C. tarsalis* in Central Valley, California, but its role is undetermined. There appears also to be a close association with the St. Louis disease as they occur in the same area, often simultaneously.

Reeves and associates have isolated 13 strains of this virus from 130,000 bird mites (*Bdellonyssus sylvarum* and *Dermanyssus gallinae*) collected in Kern County, California, of which nine were identified as Western and four as St. Louis encephalitis.

The avian hosts were sparrows, yellow-headed and other blackbirds. There was no correlation between immunity in the bird and presence of the virus in its ectoparasites. Chamberlain found that the virus could be detected in *D. gallinae* up to nine days after feeding. The incubation period is 4–21 days and the clinical picture is similar to that of St. Louis encephalitis.

Prevention.—Although formalized vaccine is available, its use is not advised, except for laboratory workers exposed constantly to infection.

(4) **Eastern equine encephalitis** (Epizootic equine encephalomyelitis).—This is a neurotropic virus disease of equines and birds, transmissible to humans and birds. It broke out in the summer of 1933 in N. America. Ten Broeck and Merrill, Shahan and Giltner (1934) isolated it from brains of infected animals and later Forthergill and colleagues did the same in man (1938). The Eastern virus is distinct from the Western and causes a much more severe disease. In the summer and autumn of 1938 a severe epidemic in Massachusetts caused a severe illness in 44 people, as well as in many horses and mules. There was a high fatality rate. It has been found in the Eastern portions of Canada and the U.S.A. as far West as Ontario and Michigan. As the virus is transmitted by mosquitoes, with the probability of bird reservoirs, contact with horses would not be important. Birds have been found susceptible under experimental conditions. The virus has been recovered from pigeons and pheasants. *Aedes* mosquitoes were suspected as transmitters, especially *A. sollicitans* and *A. vexans*.

In contrast to the Western type, macroscopic findings disclosed pulmonary oedema and visceral congestion. As a rule, the disease is very severe and fulminating, with an abrupt onset. At first there is nausea, vomiting, headache, and high fever for 24–36 hours, succeeded by a short remission. The first phase is followed by severe second phase with high fever, drowsiness, opisthotonus, marked muscular rigidity, paralysis, convulsions, coma and cyanosis.

Prevention.—Formalin-inactivated vaccines are available and have been used successfully in controlling the disease.

(5) **Venezuelan equine encephalomyelitis** (Peste loca).—This is primarily a neurotropic virus disease of animals transmissible to man and occurs in a mild form. The infective agent differs immunologically from that which causes the W. and E. varieties of encephalitis.

It has been reported also from Colombia, Ecuador, Panama and Trinidad.

The human cases so far reported have been mild. Two fatalities were registered in Trinidad in 1944.

There is no doubt that it is due to a virus which is distinct from the others.

(6) **Russian Spring-Summer encephalitis** (EEE Virus).—A widespread and fatal form of encephalitis has been described and investigated by Pawlowsky and his Russian colleagues in Mongolia and Far Eastern territories in the scrubby wastes (Taiga country). It also occurs in the Urals, Karelia, the Eastern Ukraine and White Russia in thickly wooded valleys and in areas where reafforestation is being carried out. This disease has distinct seasonal incidence, and 80 per cent. of cases occur in May and June. A somewhat similar disease has recently been reported from Mysore, India. An apparently identical virus was isolated from *Ixodes granulatus* from forest rats in Malaya (Smith, 1956).

Ætiology.—This form of encephalitis has been shown to be due to a filterable virus transmitted by the bite of a tick (*Ixodes persulcatus*), in which the virus persists, as it is found infective in wild districts uninhabited by man. The virus has been isolated by Silber and Soloviev (1946) from the brains of various species of wild animals indigenous to the country:—*Eutamias asiaticus orientalis*, *Eutamias rufocampus arsenjevi*, *Microtus michnoi pelliceus* and *Cricetulus furunculus*; these therefore constitute a reservoir of infection. Seasonal incidence of the disease during May and June corresponds with maximum prevalence of *Ixodes persulcatus*. The infection transmitted by bite of the tick is hereditary, and therefore larvæ and nymphs are also infective. The virus particles measure 15–25 m μ and are recovered from the blood, the cerebrospinal fluid, brain, liver and spleen of infected patients. The virus can be grown in tissue culture or in developing chick embryo. A formolized vaccine is of prophylactic value. Russian observers claim good results from immune serum given very early in the disease: 10–15 ml. of serum are injected into the spinal canal and 30–50 ml. intramuscularly; this latter injection is repeated two or three times at intervals of 24 hours.

Symptomatology.—The incubation period is 10–14 days. There are three clinical types (1) abortive infections of short duration (3–5 days), (2) moderately severe infections of brain and meninges lasting 2 months with neurologic and psychotic sequelæ, and (3) severe fulminating type of meningo-encephalitis. This form of encephalitis has an abrupt onset and runs a severe course with steep rise of temperature, severe headache, and vomiting. Symptoms of meningeal involvement are followed by signs of focal lesions in the central nervous system, paresis and paralysis of upper or lower limbs or muscles of the neck or back, especially of the shoulder girdle. Parkinsonism never occurs. The case mortality is about 30 per cent.

Pond and Russ have found that the viruses isolated during the epidemics of meningo-encephalitis occurring in Austria and Yugoslavia in 1953, and which were examined by cross-neutralization tests in mice, were found to be closely related to Russian Spring-Summer, Colorado tick fever, louping ill and Czech encephalitis viruses.

KYANSUR FOREST DISEASE

A new virus affecting monkeys—the black-faced or langur (*Pithecus entellus*), the white-faced or bonnet monkey (*Macaca radiata*)—and man, has been discovered by Work, Trapido and associates (1957). At present the disease is limited to the Shimoga District of the Mysore State. The virus has been isolated from patients five days after exposure and appears to belong to the Russian (R5SE) virus complex, but the symptoms in man suggest its affinity to the hæmorrhagic fevers. It has been recovered from blood and cerebro-spinal fluid, and, when injected into infant mice, produces limb paralysis on the third or fourth post-inoculation day. Serological investigation on patients in the acute stage with brain antigen were positive. In man this infection produces pathological changes in the liver and kidneys. The symptoms, so far as can be ascertained, are those common to many similar viruses. The onset is sudden; eyes red and injected with headache, backache and limb pains. Distinctive are hæmorrhagic and vesicular lesions on the palate. The lymph glands may be enlarged. Epistaxis, hæmatemesis and melæna may ensue. In the early stages there is a marked leucopenia which persists to the time of recovery and is almost diagnostic. The fever itself lasts five to ten days and then, as in other virus diseases, falls abruptly.

(7) **Encephalitis japonica.** *Synonym.* — Japanese Type B encephalitis.

Japanese Type B encephalitis is an epidemic encephalomyelitis involving the brain and spinal cord; it is to be distinguished from epidemic encephalitis (Von Economo's disease) by the absence of eye lesions and other features to be detailed later, and from the autumn encephalitis in Eastern Siberia. It is now recognized as caused by a virus related to that of the Australian X disease or "Murray Valley Encephalitis".

Epidemiology and geographical distribution. — Encephalitis japonica, as its name implies, is well known in Japan, where it apparently has occurred in epidemic waves since 1871.

During recent years it has also appeared in China, and in the summer of 1938 there was an epidemic in Peking. Cases have also been recognized in Shanghai, Amoy and Tientsin. It is now known to have a much wider distribution than was at first believed. It has been diagnosed in Korea, Formosa, Ryokyu Islands, in the maritime Krai and in Siberia also. In Japan most of the cases occurred in children, but in Pacific Islands, such as Okinawa, it attacked American troops during the second world war and appears to be endemic in natives of that island. Neutralizing antibodies were found in the blood of Okinawan horses and goats, but not in chickens. There is evidence of the infection in Malaya (Hale, 1955) as well as in Madras (Work, 1956).

Ætiology. — Knowledge of the virus of this epidemic encephalo-myelitis comes from Kobayashi, Takaki, Nishibe and Hayashi. Credit is due especially to the latter for his important researches on its transference to monkeys, in which it produces the same histopathological lesions as in man. In America, however, white mice have been found more susceptible than monkeys. Webster and Fite demonstrated that the virus, which is active in the blood and in the central nervous system in the early stages, can be inactivated by convalescent serum. It can be cultivated in hens' eggs. The virus was isolated by Kasahara and colleagues, Kawanamura and colleagues (1936) and Taniguchi in 1936.

The transference of the virus from man to man is by mosquitoes. The following species transmit the virus and have been found infected in the field: *Culex tritaeniorhynchus*, *C. pipiens* var. *pallens* and *Aedes togoi*. Another Japanese *aedes*, *A. esonensis*, readily transmits by biting, as do the following North

American species: *A. nigromaculis* and *A. lateralis*. *Culex pipiens* and *C. fatigans* (*quinquefasciatus*) are also capable of transmitting by bite. In Okinawa, however, *C. fatigans* did not appear to be the vector. There is also an analogy with equine encephalomyelitis, which has been observed in horses as well as in man and which is transmitted in this manner. In Japan it occurs in the summer and autumn. Perdrau, by using hyperimmune sera, was able to demonstrate antigenic relationship between the virus of encephalitis japonica and that of St. Louis. The dimensions of the virus particles are estimated at 25 m μ . This virus may be transmitted by blood transfusion.

Antibodies to Japanese B. encephalitis virus have been found in the sera of domestic animals (horses, cows, pigs and goats).

Antibodies to the virus of the related Australian form (X disease) have been found in the sera of wild birds in the Murray Valley.

Symptomatology—The incubation period is 6–8 days. Onset is gradual or acute with fever (T.104°), extreme rigidity and exaggerated reflexes. The prodromal symptoms commonly encountered are headache, dizziness, sluggishness, and vomiting. These are followed by psychical disturbances, very often by delusions, but in very severe cases coma ensues, ending in death. The psychical signs and symptoms may be entirely absent in the mild cases, and (in contrast with encephalitis lethargica) meningeal symptoms may predominate. Disturbances of the motor system are characteristic: there are clonic contractions of the muscles which may end in actual convulsions. Fine tremors of individual groups of muscles alternate with attacks of shivering and athetoid movements. The whole muscular tone is increased in the extremities and in the neck and face, especially the masseter muscles, which results in an anxious expression, and ends in trismus making mastication impossible. In very advanced cases, encephalomyelitis causes paralysis of the spinal cord, but, in direct contrast to encephalitis lethargica, eye symptoms are absent; nor is post-encephalitic Parkinsonism ever observed, though bulbar symptoms, resulting in failure of speech and difficulty in swallowing, are quite common and, in addition, defects in co-ordination and sometimes even cerebellar disturbances. Anomalies of superficial and deep tendon reflexes are usually present, especially in *spastic* cases. Salivation and excessive sweating are absent. Ocular manifestations, such as diplopia, nystagmus and photophobia, are not uncommon. In patients who recover lysis occurs within a week. The disease is fatal in approximately half the cases of overt infection, but there is evidence that inapparent infections are frequent. (Fig. 135).



Fig. 135.—Male of 5 years with Japanese B. encephalitis, 40th day of illness.
(W. Hammond.)

The foregoing description covers only the main features, however; actually the clinical picture is a many-sided one. There is also another aspect to this disease in that, though the neurological side dominates the picture, there is a secondary affection of the hæmopoietic organs, resulting in a secondary anæmia, which appears to indicate a generalized infection, rather than a local affection of the central nervous system. As a rule, the temperature chart is not characteristic, and the course is afebrile. There are cases, however, in which fever is noted for five to ten days, and these are followed by sequelæ, such as profound neurasthenia. The fulminating cases, which are fatal in twenty-four to forty-eight hours, are generally pyrexial. It is to be noted that there are no pupillary or eye symptoms, and there is no special affection of the bladder or bowels. Usually there is at first retention, followed later by incontinence.

Diagnosis.—The main points in differentiation from Von Economo's disease have been noted. The cerebro-spinal fluid shows all grades of inflammatory disturbance. Kaneko and Aoki have shown that there is an increase of the protein content from 9 to 350 mgm. per cent. A mouse-protection test or that for hæmagglutination—inhibiting complement-fixing and neutralizing—may be used for diagnosis. Differential diagnosis has to be made from lymphocytic choriomeningitis.

Pathology.—Epidemic encephalomyelitis is characterized by diffuse lesions in the brain and spinal cord: these take the form of small white knob-like aggregations of cells, composed of microglia intermingled with lymphocytes and leucocytes. Here and there ganglion cells are also found acutely damaged.

Treatment.—No specific treatment is at present known, but a vaccine made from formalized mouse brain has been used by Sabin for the immunization of American troops and exposed natives. More than 300,000 persons have been given two to three doses of mouse-brain vaccine. The virus has been adapted to eggs.

Prophylaxis.—Solid protection against apparent infection with Japanese B. virus is likely to be secured, for neutralizing and complement-fixation antibodies are found early in the disease. The former appear as early as the third day of symptoms. Russian workers have used a mouse-strain and chick embryo vaccines for a number of years with promising results. They have also been given in Okinawa, inapparent infections are common, many persons acquiring neutralizing antibodies during the epidemic season.

ACUTE ANTERIOR POLIOMYELITIS

Synonym.—Infantile Paralysis.

Epidemiology and geographical distribution.—As an endemic infection poliomyelitis has been found all over the world. In epidemic form it has been reported from N. America, Scandinavia and Australia. In the second World War serious outbreaks occurred in Malta, St. Helena, Mauritius and N. Africa, but the highest incidence in British troops was in India and in the Middle East. In *Central and S. America* outbreaks have been recorded in Argentina, Brazil, Colombia, Costa Rica, Ecuador, San Salvador, Mexico, Nicaragua, Panama, Porto Rico, Uruguay and Venezuela. In the *West Indies* it is endemic in Barbados, Jamaica, Tobago and Trinidad, Egypt, Palestine and Malta.

In *Central Africa* it is reported from the Congo, French Equatorial Africa and W. Africa, especially in the rainy season. In E. Africa it is found in Kenya, Tanganyika and Uganda, and also in the Union of S. Africa, St. Helena and Mauritius. It is endemic in India, especially in children; and in Japan, China,

Indochina, Malaya (as in Singapore 1945-1946). In Australia epidemics have been reported as well as in New Zealand.

Age and race incidence.—Outbreaks have affected predominantly those under 5 years of age. Hence the term "infantile paralysis." Those in warm climates are held to represent an epidemic "flare up" of an endemic infection. A noticeable feature of urban poliomyelitis during the last 30 years in the U.S.A., Australia and Scandinavia, has been the greater tendency to involve school children, as opposed to the pre-school child, thus resembling measles and diphtheria. Adults are not commonly attacked.

RACE.—Certain coloured races seem to be less susceptible than white people. In the U.S.A. the reported incidence of the latter is 3-4 times as great as that in coloured people. In 1945 in Mauritius the Chinese showed the highest incidence. In Malta cases occurred in British troops, but not in the Maltese.

Other considerations.—Many observers have referred to a higher incidence in country districts than in towns and cities. There is a tendency for cases to occur predominantly in summer and autumn in the N. hemisphere and in the first four months of the year in the S. hemisphere. In recent years contact in the home seems to play an important part in the distribution of poliomyelitis. Familial infections are commoner when exposed children are young than when they are over 10. As the virus occurs in faeces it is possible that it can gain access to water supplies, so that polluted water has been found to be responsible for infection of sporadic cases in U.S.A., whilst a number of outbreaks have been definitely traced to milk.

Ætiology.—The poliomyelitis group of viruses are composed of the most minute particles yet discovered.

The terms—human, murine and porcine types—have been proposed by Gard (1943). The bulk of the strains are transmissible to monkeys and chimpanzees, but cannot be adapted to rodents. One of the most important is the Lansing strain of Armstrong isolated in monkeys in 1939. SK strain of Jungeblut and Sanders was isolated from the faeces of abortive cases by monkey inoculation. This is adapted for mice and has lost its virulence for monkeys. M.E.F.1 strain was isolated in rhesus monkeys and infects cotton rats and mice. The M.M. strain of Jungeblut and Dalldorf (1943), causing paralysis of albino mice, cotton rats and hamsters, originated from the brain of a mouse.

The virus is found in the oropharynx for three to five days before and from three to seven after the onset of the illness: it may also be present in this situation in persons exhibiting no signs of illness. In three weeks from the onset most patients have ceased to excrete the virus in the faeces.

The virus is very sensitive to dessication and is destroyed at temperatures over 60° C. Application of heat is probably the most practicable means of disinfection of materials: Resistance to chemical agents—alcohol, acetone, formalin, etc.—is very considerable.

Antigenic relationships in the poliomyelitis group.—Antigenic differences have been noted between freshly isolated human strains of the virus and those passed for some time in monkeys. Freshly isolated human strains also vary from one to another, but S.K., M.M. and Lansing strains are related. After inoculation by any route, monkeys and chimpanzees may suffer from non-paralytic attacks, but recover before paralysis sets in. The virus has not been detected in blood or urine, but has been frequently isolated from nasopharyngeal mucosa as well as in tonsils and adenoids, and it may persist for two weeks. The virus has been found in the faeces two days after onset and probably all cases excrete it during the first week and may continue to do so for 50 days.

Three immunological types of poliomyelitis virus have been identified, the prototype strains which are known as Brunhilde (Type I) Lansing (Type II) and Lion (Type III).

Carriers.—It is now clear that the virus is widely distributed in the environment of abortive or paralytic cases. Whilst some contacts develop the abortive type, the majority are in good health, but carry the virus for the same length of time as do sufferers from poliomyelitis. The majority of positive isolations have been from children. Even infant contacts may be healthy carriers. Persons harbouring the virus in the nasopharynx may later develop poliomyelitis.

Clinical pathology.—Examination of the cerebrospinal fluid is important, especially in the preparalytic stage. The fluid is usually under increased pressure and hazy. There is an increase in cell count but the greater number of cells are to be found in the first week after the onset of paralysis. There are seldom over 100 cells per cmm., composed mostly of lymphocytes, but in the early stages polymorphonuclears may constitute 50 per cent. of the total. The total protein becomes increased, reaching its maximum in the third week. The colloidal gold curve, is of the luetic or meningitic type.

Fehling's solution is always reduced, but there is no significant change in the chloride content. There is a blood leucocytosis up to 25,000 per cmm. in the paralytic stage and there is usually a 15 per cent. increase in the polymorphonuclears.

Acute anterior poliomyelitis in man.—Wickman's work on epidemiology (1907) suggested that the disease was infective. It soon became apparent largely by the work of Flexner in America that the pathogenic agent was a filterable virus. In a large number of cases bulbar or bulbo-spinal poliomyelitis has developed within 7–30 days of tonsillectomy or adenoidectomy. Tooth extraction may precipitate an attack and there is little doubt that pregnancy predisposes to it. Incubation period is 7–14 days with 5–35 days as outside limits.

Illness and infection.—*Non-paralytic poliomyelitis.*—There may be a transient minor illness at about the time of the presumptive date of infection. This is characterized by naso-pharyngitis, fever and headache. After 1–2 days the patient recovers and appears well for 4–7 days when fever returns and paralysis supervenes. This is termed "dromedary" type of illness. In any epidemic there are likely to be several times as many non-paralytic as paralytic cases, especially in those under 16. Diagnosis of poliomyelitis in the preparalytic stage is difficult.

Preparalytic poliomyelitis begins in various ways and fever is usually present for 1–4 days. Catarrhal symptoms are common with sore throat, tonsillitis and nasopharyngitis. Frontal headache is frequent, but in other groups the onset may be accompanied by gastro-intestinal symptoms.

Pain is elicited by any effort involving movements of the spine. Stiffness in neck and back and resistance to anterior flexion are common. These can be tested by pulling forward the head of the child, who then complains of pain, and rigidity is experienced by the observer; but when the shoulders are raised, the head usually falls back to the bed. Amoss', or the "tripod sign" is elicited by asking the child to sit straight up in bed, when he will place his hands on the bed behind himself for support. Kernig's sign is often weakly positive—muscular tremors, when present, usually heralding the site of forthcoming paralysis. The child is usually irritable and restless, but apathy and stupor may occur together in some and there may be encephalitic symptoms.

What are known as Phase I symptoms are thought to be due to involvement of the brain stem and basal nuclei. The patient may be drowsy, listless, restless

or irritable. The sleep rhythm may be inverted. Even at this stage there may be changes in the C.S.F. Some cases may not develop any further. In Phase II the thalamic and hypothalamic disturbances persist. The virus spreads nearer to the cord and symptoms develop owing to involvement of the posterior columns. The neck is stiff and rigid. There is muscular ataxia and tremor whilst reflexes are increased. Pains may be spontaneous and are due to the involvement of the posterior columns and root ganglia: not to meningeal irritation.

Associates of cases of poliomyelitis are frequently met without showing any clinical evidence of this process. Such infections are known as *inapparent*, asymptomatic or silent and can be recognized only in the laboratory by recovery of the virus or by the demonstration of an increase in serum antibody. Others go on to develop minor illnesses characterized by headache, fever, etc. as described above.

Paralytic poliomyelitis.—This usually develops after one to four days of non-paralytic illness which may be very brief. The commonest types are the ordinary or spinal, the polio-encephalitic and the bulbar and bulbo-spinal types: cranial nerve paralysis has been noted more commonly in some outbreaks. Paralysis is flaccid, but the distribution is often asymmetrical: for instance one leg and the opposite arm; the cutaneous sensation is normal, the reflexes are absent in the affected limbs. The sphincters are unaffected. Recovery of movement may continue for three months. One leg is most commonly affected and next one leg and one arm. In lower extremities extensors of hip, knee and dorsi-flexors of ankle are most affected, and in upper extremities the muscles of the shoulders. The abdominal muscles are but uncommonly affected in young children. During the stage of recovery permanent results become obvious, such as shortening of the affected limb, and deformities, such as talipes, flexed knees and occasionally scoliosis and lordosis.

Diagnosis.—The cerebrospinal fluid should be examined for cell count and estimation of protein. If the case is fatal, part of the cord should be retained for histological examination and the remainder should be placed in 50 per cent. glycerol for subsequent monkey inoculation. During convalescence the serum may be examined for the virus (neutralization test).

Differential diagnosis is important. Abortive poliomyelitis may resemble serous and lymphocytic choriomeningitis, simple infections of the upper respiratory tract, sandfly, dengue and dengue-like fevers. Many children diagnosed as "meningismus" are in reality abortive poliomyelitis.

Prognosis.—It is possible to estimate approximately the general prognosis in cases suffering from suspected poliomyelitis during an epidemic—of every 100 such, 5 or 6 are likely to die, 7–10 to be severely paralysed, 17 or 18 to have some degree of residual paralysis, 35–40 to suffer no ill effects or to be left with a slight degree of disability in one third of cases in children under 5, one third in children of school-age groups and one third in persons above 15.

Prophylaxis.—*Notification* is practised in almost all countries and non-paralytic cases should be as fully reported as paralytic ones. Patients in whom the disease is either abortive or paralytic are isolated for three weeks. All evidence suggests that poliomyelitis virus is very infective and is spread by pharyngeal and intestinal excretions. Contamination of hands, utensils and food by pharyngeal virus may be involved. In an infected family, most members become infected about the same time.

During the epidemic periods gatherings of children should be forbidden. In rural areas schools must be closed, but in urban areas it is doubtful whether

school closure is of any value. Water supplies must be chlorinated. Urine, faeces, and soiled linen must be sterilized by carbolization. Bathing in streams, lakes or even in chlorinated water in baths, must be forbidden.

PROPHYLACTIC INOCULATION.—The British formological vaccine contains the Brunender's Type I, MEF-J type II, and Saukett type III strains. Although the number of observations at present is small, there appears to be no doubt that the Brunender's strain confers protection against type I infections prevailing in Britain. Vaccinations were carried out by local authorities in clinics from May to June, 1956. 48,684 children received two injections with an interval of not less than three weeks between them.

There is no evidence that the injections are accompanied by any risk. Local reactions are mild. In both age groups, $1\frac{1}{2}$ – $5\frac{1}{2}$, and $5\frac{1}{2}$ – $9\frac{1}{2}$ years the observed incidence of paralytic disease in vaccinated children was only one-fifth of the incidence in the unvaccinated.

In the first group the attack rate was 4.1 per 100,000 and in the corresponding unvaccinated group 20.1 per 100,000. In the second group it was 1.3 per 100,000 as against 8.2 per 100,000 in the unvaccinated. Since some cases of paralytic disease were observed in the vaccinated children, in the form in which it was given, it did not therefore offer complete protection.

LĀTAH, RUNNING ĀMOK AND KORO

Kuru is the native name for a strange disorder of the central nervous system endemic in the newly-explored area south of Mount Michael in the Eastern Highlands of New Guinea. This *trembling disease* affects females, chiefly, and is inevitably fatal within a year. It is specially known to the Fore tribe as their special curse, for at least 20 years, and it has recently been observed in adjoining tribes. Zigas and Gajdusek (1957) have recorded their findings in 150 cases. It has been found also in a few women from communities with a low incidence of the disease after entry into a "kuru" area and the fact has to be satisfactorily explained before it can be accepted that this is a genetically determined disease. The male/female ratio is 1.5/42. In 23 per cent. the patient's age is less than 15. About 1 per cent. of the total population is at present affected, but in some districts the figure may reach 10 per cent.

The onset is insidious with ataxia. Prodromal symptoms are knee pains, headaches, fever, cough and coryza.

As ataxia progresses a distinctive tremor appears, irregular, but fine, involving head, trunk and limbs, exaggerated by excitement or fatigue. It subsides during relaxation and disappears during sleep.

Movements are aggravated by excitement. In the second or third month the tremors coarsen and interfere with work and sleep.

Choreiform jerks with wild athetotic movements occur, especially when the patient tries to stand. Emotional behaviour may be prominent with moods of depression.

Progressive dysarthria sets in with convergent strabismus, flexed posture and Parkinsonian facies.

Soon most usually the woman is confined indoors, mute and doubly incontinent and rapidly succumbs to starvation or intercurrent infections.

The course of the disorder is from three months to two years with an average of six to nine months. There are no physical signs other than those referable to the central nervous system. The fundus oculi is normal and the pyramidal tracts are not involved. The cerebrospinal fluid has not revealed any abnormality except an occasional positive Lange curve. Pathological findings are confined to the nervous system. There is widespread neuronal degeneration with neuronophagia, affecting especially the cerebellum and extrapyramidal system, to a lesser extent the anterior horn cells, the inferior olives, thalamus and pontine nuclei. The Fore people who are affected with kuru live in a heavily forested region covered with kunai grass, at an altitude of 5,000–7,000 ft.

According to the most recent communication of Bennett and Rhodes (1959) "kuru" occurs most frequently in daughters of mothers recorded as dying from it—about one-half of all deaths from this disease occurs as such, as against less than one-quarter of deaths of sons of affected mothers. These facts have given rise to the hypothesis of a single autosomal mutant *gene* which is dominant in females, but recessive in males.

This aspect is antagonistic to the hypothesis that selection against the *trait*, the phenotype, is high, in face of severe selection to satisfy the genetical hypothesis that such a high *gene* frequency could be maintained by fresh mutations.

Lātah, a word signifying "nervous" or "ticklish," is not uncommon in the natives of the Malay Peninsula, Java, and the neighbouring islands. It occurs more frequently in women, especially young women, than in men; children are seldom affected; it rarely appears before puberty and is especially common at the menopause.

A somewhat similar affliction is described among the Ainu people, usually in women, and is known as *imu*. This manifests as psycho-motor attacks precipitated by some emotional shock. If a sufferer is startled, she may continue to echo everything that is said to her.

Lātah persists for years. The main characteristics of this state are the same, though there is considerable variety in the intensity of the symptoms. The condition is incurable, shows no tendency to become worse, and does not terminate in insanity.

As the Malays say, an *orang lātah* never becomes an *orang gila* (âmok). The subjects of "lātah" at first appear to differ in no way from their neighbours and relations, but on some sudden and striking impression, such as a loud sound, or in response to some overt suggestion by word or deed, they pass into a peculiar mental state in which they involuntarily utter certain sounds and execute certain movements. In other instances they will imitate words or movements, or yield to suggestions from others. During this hypnotic-like state, which may last for a few minutes or longer, the victim is at the mercy of his prompter and will unerringly follow any lead indicated. Although the manifestations of high degrees of lātah may be followed by exhaustion, or even by swooning, as a rule nothing of the kind occurs. The infirmity is usually discovered by accident. Swettenham, for instance, used to relate that it was only necessary for anyone to attract the attention of these men by the simplest means, such as holding up a finger, or calling them by name in a pointed way, touching them, or looking them steadfastly in the face, in order to make them lose control of themselves and be willing to execute whatever was suggested by a sign. On one occasion, one of them, on being told that a roll of matting was his wife, embraced it with every sign of affection; but when the other lātah subject, a policeman, was convinced that the same roll was his wife likewise, he too embraced it, and the two men fell to the ground struggling for the possession of the "lady."

Lātah folk are favourite subjects for the practical joker, and in a few instances they very much object to being made a show of, and may become dangerous. Lātah seems to be akin to certain emotional stresses which are common in all barbarous and semi-civilized countries.

Abraham has seen the afflicted, if suddenly startled, fall down and imitate the gestures of anyone in sight; for instance, an old lady startled by a bicycle bell, will instantly imitate the pedalling of the cyclist till exhausted.

The most profound study of the pathodynamics of lātah from the modern psychological aspects has been published by Yap (1952). From this it appears that lātah reaction is related to "sleep intoxication" and the so-called "startled neurosis," and is to be differentiated from convulsive tics or "primitive hysteria." A special modifying of personality and the organization of fear in persons belonging to cultures of low technological level are suggested. He has drawn attention to the resemblance of lātah to the "jumpers" or "shakers," a group of religious people, originating from the Methodist congregation of Wales

during the time of the evangelist, Whitefield. They practised ritualistic jumping and shaking to the accompaniment of incoherent gutturals.

Unless unforeseen accidents occur, *lâtah* is not fatal. Gimlette and others have called attention to the medico-legal aspects of the disease. Fortunately, examples in which *lâtah* has been shown to play a part in crime are rare. Temperamentally, all the Malay races are very highly strung and nervous, although externally impassive, and there appears to be an hereditary tendency to the *lâtah* state in every Malay.

Young-dah-hte is a state closely related to *lâtah*. Mongolian races are predisposed. Heredity does not seem to play any part. It differs from *lâtah* in that the patient continuously remains in the imitative condition and is always liable to reactions.

Nat-win-de is a religious dance with closed eyes and swinging movements. It is started by professionals and taken up by others.

There appears to be a somewhat similar affection amongst the Samoyedes which is known as "*Ikota*," and it is believed that the curious epidemics of religious ecstasy, which swept over Europe during the Middle Ages, were of similar origin.

Mirzacht is a hypnagogic intoxication seen in Siberia and has been compared to "*Schlafrunkenheit*" and is practically the same as *Ikota*.

Banga is a hysterical affliction in Congo women at puberty. The subject is convulsed and rushes about uttering wild cries.

"*Âmok*" (or running *âmok*) is a term used somewhat loosely for a condition which, in the fully developed form, drives its victims to blind fury and to kill without reason.

Usually the "*âmok*" runner (or *âmoker*) has a grievance upon which he allows himself to brood, and after a period of sullenness decides to kill the suspected person and at the same time to destroy as many other people as possible. He therefore arms himself, runs "*âmok*," and buries his *kris*, when out to slay, in friend and foe alike, with the expectation of being killed in turn.

In other cases there may be premonitory signs in which a person mutters and has delusions. Quite suddenly he will run "*âmok*" and after the attack may fall into a deep slumber and become comatose. The liability to "*âmok*" attacks is greatest in the Malays and their drugs, such as Indian hemp (*Cannabis indica*), are known to be potent predisposing causes of the attack. Van Loon found that in Java "*âmok*" runners are often suffering from some infectious disease, and that the symptoms are hallucinations and confusion; such patients are impelled to flight and attack as reactions to imaginary dangers and the agony and terror caused thereby.

"*Koro*" occurs amongst the Macassars and the Buginese in Celebes, and is also well known among the Chinese as *Shook Jong*, originally described by Blonk in 1895. The term signifies "shrivelling," and a feeling occurs at regular intervals of the penis retracting into the abdomen; if help is not forthcoming the patient dies. In his anxiety, the patient grasps the penis, and if unable to do so, obtains assistance from others. It may be days before the attack subsides, and the sufferer cannot bear to be left alone. If help be not to hand, he will actually tie the penis to his leg with string, anchor it by means of a pin, or may even employ a double-bladed clasping instrument known as *li teng hok*, which is used by jewellers. By the native this tendency is regarded as the "*Yin*" principle, representing the female power, dominating the "*Yang*" principle, which

represents the male element. In order that a "Yin" disease may be cured, a "Yang" medicine must be employed. The sufferers are generally neurotics, and the anxiety arises out of sexual conflicts. Various pathological conditions, such as cedema of the lower abdomen, hernia, hydrocele and elephantiasis of the scrotum, may evoke fear of an attack. An analogous state, characterized by diminution of the genital labia and shrinkage of the breasts, is known to occur in women.

CHAPTER XXXIX

NEURASTHENIA IN THE TROPICS

PSYCHONEUROSES play a considerable part in adding to the burdens of life, and are the cause of a proportion of invaliding among European officials and business men from the tropics ; more especially from West Africa. As a cause of disability, neurasthenia or anxiety psychoneurosis, or whatever term may be applied to this real and distressing condition, has superseded tropical diseases. Therefore, from the point of view of Colonial Administration, neurasthenia is of greater importance than the majority of the tropical diseases with which this book deals. There is nothing peculiar to tropical neurasthenia which differentiates it from similar anxiety neuroses in temperate climates.

When it is considered that, in the figures quoted by Squires, no less than 45 per cent. of 353 invalidings of Europeans from the tropics were for psychological reasons, there is obviously some feature in life under tropical conditions which predisposes towards this state. Fully developed and frank neurasthenia, as seen in its most characteristic form, is more apt to develop in a neurotically-disposed individual than in one of a complacent and unemotional mental make-up, and it is not always possible to gauge with accuracy those individuals in whom tropical neurasthenia will eventually develop. Culpin pointed out that certain persons go to the tropics as a flight from the strain of social life at home.

In an analysis of neurasthenia in West Africa, Rowland Hill (1943) found that patients with long-standing conditions of nervous instability were made worse by tropical life, but in nearly all there was evidence that the neurasthenic tendency had been exaggerated by illness acquired in the tropics.

The influence of tropical infections.—Tropical infections, especially the enervating, debilitating, and irritating recurrent relapses of malaria, are predisposing factors. The recurrent headaches and fevers encourage patients to refer sensations to the cranium, so that they complain of neurasthenic headache, lack of concentration, loss of memory (West Coast Memory), and general disinterestedness in life. Intestinal infections, such as amoebic or bacillary dysentery, may promote concentration of thought on the intestinal tract. The patient's attention becomes riveted on his digestive system, with the result that introspective psychoneurosis develops. In this respect tropical infections do undoubtedly predispose to "tropical neurasthenia." But there are other aspects of life in the tropics which engender introspection. The heat, the proximity to natives who cause annoyance and whose ways and psychology the European cannot understand, the dull monotony, the ever-recurring twelve hours of daylight alternating with twelve hours of pitchy night, and the abundant and vexatious insect life ; all act as stimuli which goad to the neurasthenic state. The dulling of the appetite engendered by heat, the unpalatable and unsuitable food, the greasy cooking, the abundance of starchy matter, the monotony of tinned foodstuffs, together with the comparative absence of essential vitamins, all tend to upset the digestive apparatus and to depress the higher psychical centres.

Fear of disease and hypochondriasis are sources of neurasthenia in previously healthy and well-balanced people who, after serving in the tropics for long periods, have suffered a good deal of illness without much deterioration, but with loss of confidence in their ability to stand tropical life. All those who have a tendency to anxiety neurosis are made worse by exposure to heat.

Sleep.—Insomnia, which is the outward manifestation of physical exhaustion, and which nearly always appears towards the end of the tour in tropical Africa, is usually the first manifestation of the neurasthenic state, and imperatively indicates invaliding to a temperate climate.

Sexual factors.—Other factors will occur to anyone who has lived in isolation under tropical conditions. There is the sex factor, which may be potent; there is the social isolation which operates in out-stations; in others it is excess of alcohol, late hours, or living an unaccustomed life attended by native servants—all these may upset the mental equilibrium. Then there is, too, the constant restraint and watchfulness required to avoid offending against local prejudices, and having to live with others who are also in a state of constant exasperation.

Work and exercise.—Probably hard mental and physical work, in moderation, act as a bar rather than as a predisposing factor in the development of neurasthenia. Mental occupation tends to divert the mind from self-interest. On the other hand, mental pressure or undue stress appears to be less easily tolerated in the tropics than at home. Neurasthenia is not a special affliction of Europeans, for it is frequently observed amongst the educated native officials in West Africa, Malaya and India, though the proportion is by no means so great as in Europeans.

Neurasthenia in women.—It is difficult to state the sex incidence of neurasthenics; probably women, with their more highly developed emotional centres, are more apt to develop it, granted equal opportunities, than men.

A tropical climate usually produces certain psychological effects in women. Those who become neurasthenic suffer from pelvic pain and discomfort, menorrhagia and toxæmia. Constipation, by favouring pelvic congestion and inflammation, and uterine displacements, have also to be considered.

The effect of the tropical climate on the newly-arrived European woman is at first distinctly exhilarating. The appetite is increased and the heat does not oppress her at first as it does in succeeding years, and she has a feeling of well-being. Menstruation frequently stops for a season. The sense of well-being may be so real that risks are taken which more experienced residents avoid, such as eating unsuitable food. The long hours that European women spend in shaded houses during the heat of the day engender a feeling of lethargy, due to extra work thrown on the liver, and want of exercise.

Childbirth in European women in the tropics is apt to be more difficult and laborious than in temperate climates, due very probably to the conditions of life; but even among native women between 30 and 40 per cent. of deaths are directly or indirectly connected with parturition. Native women, as a rule, give birth with extraordinary ease, and only where they have departed from a natural mode of life, and are living in seclusion, is parturition difficult.

The effect of tropical conditions.—Tropical life may have a disturbing effect on the mentality of even the most healthy and balanced individual. After a year or more of constant exposure to heat and humidity, the hours of sleep become disturbed, and the nervous system more sensitive to external stimuli. Insomnia may be precipitated by certain electrical conditions of the atmosphere, at present little understood, skin conditions, especially prickly heat, and possibly a hyperglycæmia which Dutch investigators in Java ascribe to the climate. Otherwise healthy adults often appear "nervy" and "excitable," showing exaggerated reflexes and nervous twitchings of the face and limbs, with increased reflexes,

directly they return to a temperate climate. In the minor states of disturbance the fears and stresses disappear the moment cool headwinds are encountered, and peaceful and refreshing sleep is enjoyed once more. But transference to his home climate does not immediately relieve a fully-developed neurasthenic of his fears; on the contrary, the hum and bustle around him may act as further stimuli.

The subject of "Tropical Fatigue" assumed considerable importance during the second world war, especially amongst service personnel on land and sea, under tropical conditions. Macpherson (1949) noticed that complaints fell under the following headings (1) Loss of weight, (2) loss of energy and feeling of tiredness, (3) inability to produce efficient work, (4) increase of malaise and involvement of the skin, (5) dizziness in the erect position and blackouts, (6) anorexia, (7) loss of initiative, (8) mental dullness, (9) irritability. The sum total produces the neurasthenic state.

Symptoms.—The very appearance of the individual betrays his mental state. He (or she) is emotional to a degree, so that any sympathetic reference to health may provoke a flood of tears. There are others in whom the most profound depression reigns, and who may display suicidal tendencies; these are usually associated with intractable insomnia.

The patient usually complains of a headache confined to the temporal or parietal portion of the cranium. There is a sense of increased intracranial pressure. Others experience a sinking feeling in the abdomen, indefinite abdominal pain, or flatulent dyspepsia. There is usually a mild tachycardia, or rather vasomotor instability, with a fall in blood-pressure and a diastolic pressure below 80. The reflexes are usually exaggerated, and there may be a false ankle-clonus with hyperhidrosis of the palms of the hands and of the feet.

It has been suggested that the main symptoms are to be ascribed to hyperthyroidism, but the Editor has been unable to find any evidence for this hypothesis. With this degree of nervous instability it is not surprising to find divergence of the pupils on accommodation (Möbius' sign) which by some is considered to indicate hyperthyroidism.

Treatment.—The main principle in treatment is to remove the patient from his immediate surroundings to a temperate climate with congenial companions. Usually, on arriving in a cool climate, natural sleep sets in and fears and anxieties disappear. The neurasthenic state may be temporary. On the other hand the emotional and depressive states should be treated seriously and efforts should be made to discover some underlying infection. The Editor has on several occasions seen profound neurasthenic symptoms disappear after treatment of an underlying unsuspected malaria. If alcohol has been taken in excessive amount, it must be cut down, or prohibited altogether. Efforts should be made to divert the patient's attention from himself. Hobbies of all kinds should be encouraged and there is probably no occupation more restful and curative than fishing in Scotland or Ireland.

For insomnia, mild hypnotics should be prescribed, such as allonal, luminal, or medinal. Sleep may be induced by a hot bath or a cup of Ovaltine. As a general sedative a mixture of the following type may be prescribed, to be taken three times daily:

Ammon. brom.	gr. x (0.648 grm.)
Spirit. ammon. aromat.	℥ xv (0.888 ml.)
Syrup. aurant.	℥ i (3.55 ml.)
Aq. menth. pip. ad	℥ ss (14.21 ml.)
℥ ss three times a day after meals.	

Prophylaxis.—As the main treatment of neurasthenia entails removal from immediate surroundings its prevention is difficult. Once marked neurasthenia has developed in a European in the tropics, he should be invalided to a temperate climate and his return becomes a matter for anxious consideration. There are cases in which the patient quickly regains his mental equilibrium; but should the mental depression continue, in spite of the simple methods recommended, then permanent invaliding should be considered. The Editor is of opinion that a patient with well-marked tropical neurasthenia should never be permitted to return, otherwise the old symptoms will reassert themselves directly he arrives in his old haunts, so that after a few months he will be sent home again.

Section VI.—TROPICAL VENEREAL DISEASES

CHAPTER XL

LYMPHOGRANULOMA VENEREUM AND CAT SCRATCH DISEASE

Synonyms.—Climatic bubo; Lymphopathia venereum; Esthiomène; Lymphogranuloma inguinale; Inguinal paradenitis; Poradenolymphitis; Nicolas-Favre disease (French).

Definition.—A generalized virus infection usually transmitted by venereal infection and associated with a self-healing primary sore and changes in the lymph nodes draining the area where the primary sore is situated. In addition to these lesions the virus may give rise to a genitiano-rectal syndrome with inflammatory stricture of the rectum, to meningo-encephalitis and to eye-lesions.

Epidemiology and geographical distribution.—Scheube originally applied the term "climatic bubo" to a type of adenitis terminating in suppuration, not uncommon in tropical countries. Whether it is becoming increasingly frequent, or whether because attention has been drawn to its peculiar nature in recent years is a moot point, but recently "lymphogranuloma" has emerged from the obscure recesses of textbooks on tropical medicine into the full limelight of general medicine, so as to merit the title of the "*Sixth Venereal Disease*," which has been bestowed upon it by Stannus.

In tropical practice the disease is found especially among negroes of both sexes, both in West Africa and in North and South America. It is found, however, in seaports throughout the world.

In 1918, Durand, Nicolas, and Favre described it in France, and possibly the condition long known as the "strumous bubo" is the same.

In 1938 Stannus and Findlay described an indigenous case in England. Since then Anwyl Davies discovered others. Now numerous reports of its occurrence in Italy, Rumania, Scandinavia, and in fact the whole of Europe, are to hand. At certain times and places it appears almost to be epidemic. There seems to be no doubt that, in almost every instance, infection is acquired by sexual intercourse, normal or abnormal.

Ætiology.—Hellerström and Wassén (1930) originally transmitted the virus obtained from the pus of inguinal buboes to monkeys, intracerebral inoculation producing meningo-encephalitis. The virus, which is apparently contained in the leucocytes, consists of minute particles which can be easily seen, and were figured by Findlay (1939). They can be stained by Victoria blue, Giemsa or Castañeda's method; with Giemsa, the larger bodies take on a bluish-purple tint, while with Castañeda's stain they are reddish-purple. Larger and smaller forms of the virus particles can be demonstrated outside the cells, lying close to cell debris, in compact colony-like masses. When they are within cells the elementary bodies

may be found in the cytoplasm of either mononuclear or polymorphonuclear leucocytes. Occasionally, these groups may attain considerable size, forming cyst-like spaces; later, the cyst-wall may rupture. The larger forms have been observed in considerable numbers, chiefly within twenty-four hours of intracerebral inoculation. There appears therefore to be a development cycle of the virus which is complete in forty-eight hours. The virus particles, or granules, were first described in cells from inguinal buboes by Gay and Prieto in 1927, and similar bodies were found by Findlay in 1933. Miyagawa (1938) finally concluded that they represented the virus and gave their measurements as $0.125-0.175 \mu$, while Findlay, Mackenzie and MacCallum showed that they resemble similar bodies found in psittacosis by Bedson and Bland in 1932, larger morula-like particles breaking up to form the small virus or elementary bodies.

Willcox and Stamp (1954) found close agreement in results of 265 complement-fixation tests for lymphogranuloma and enzootic abortion in ewes in the same sera.

Intraglandular injection of guinea-pigs with the virus produces an inguinal bubo in almost every case, so that this method may be employed for diagnosis. The most reliable methods at present are Findlay's intracerebral inoculation of white mice, which produces encephalitis, and inoculation into the yolk sac of mice. Miyagawa found that a chipmunk, *Tamias asiaticus*, is highly susceptible to intratesticular and intracerebral inoculation. The virus can also be cultivated on chick chorio-allantoic membrane in tissue culture. Ravaut, Levaditi, Lambling, and Cachera devised a method of isolating the virus from ulcerative proctitis by inserting a portion of tissue under the skin of a guinea-pig. After a few days, the inguinal gland was excised, emulsified and injected intracerebrally into a monkey. In inoculated mice a characteristic train of symptoms is evolved in five to seventy days, in which weakness, paresis, opisthotonos and convulsions occur. The concentration of the virus in the injected mouse brain is not great, so that dilutions greater than 1 in 1,000 fail to give positive results.

A protection test has been devised, by mixing equal parts of serum of the lymphogranuloma patient with an emulsion of infected mouse brain, diluted 1 in 5 in normal saline, and kept for the night in the ice-chest at 4°C . Doses of 0.5 ml. injected intracerebrally do not produce encephalitis. The serum of monkeys which have recovered gives the same reaction.

Pathology.—The essential features of the pathology of the human gland consists in little pin-point epithelioid formations scattered all through the gland substance. They are made up of masses of irregularly disposed macrophage cells together with some giant cells. Höppli described localized collections of eosinophils. Subsequently tiny micro- or stellate abscesses form.

Symptoms. *Primary sore.*—Durand in 1918, and subsequently Hanschell, described a small herpetiform ulcer on the prepuce which heals in a few days; the adenitis proper does not commence until after the primary lesion has healed. Hanschell believes that the disease does not usually occur in the circumcised. The primary lesion is an erosion with clean edges, and is surrounded by a reddened zone, but with only slight infiltration and induration. The base of the ulcer is usually whitish-grey.

Adenitis.—The incubation period of adenitis is three to four weeks after coitus, but it may be as long as six weeks to two months. The disease generally commences with remittent pyrexia, which may precede the actual localizing signs, and may be mistaken for typhoid. Soon, subacute inflammatory swellings of the groin glands are noted. The inflammation may be unilateral or bilateral; while the oblique glands are most frequently affected; at times the crural glands are attacked. Sometimes one groin is affected after the other. In well-marked cases, the internal iliac glands, sometimes the lumbar glands also, can be felt enlarged and tender on deep palpation. Signs of intoxication from absorption may be widespread, producing prolonged intermittent or remittent fevers, sometimes even pyrexia of 103–5° F. Rigors, vomiting, cyanosis, even slight jaundice, and considerable pain have been noted. Rheumatic-like pains in joints and painful effusions into joint cavities may also occur as a result of absorption.



Fig. 136.—Fully developed climatic bubo in right groin, showing also small primary lesion on the corona penis. (A. H. Walters.)

The affected glands slowly enlarge to the size of a hen's egg, or even larger and after several weeks, it may be months, the swelling gradually subsides (Fig. 136). Usually, the periglandular connective tissues inflame, and the integuments become adherent until suppuration ceases. At other times fistulous tracks form, and continuously exude a clear sticky fluid. The most striking clinical feature in the male is the extensive inflammation of the periglandular tissues with comparatively little pain and suppuration. The following stages are recognized :—

(1) A firm solitary gland, with no apparent causative lesion other than a recently-healed ulcer on the genitalia.

(2) A firm solitary gland adherent to overlying skin and deeper tissues. Adjacent glands are enlarged, including external iliac glands, palpable as a mass above Poupart's ligament. The affected glands tend to coalesce.

(3) The glands in the groin soften and fluctuate. If incised, a cavity is disclosed, trabeculated by coarse, fibrous strands.

(4) The softened gland-mass ulcerates through the skin, and spontaneous fistulation occurs. Infection and extensive keloid formation may ensue.

It was formerly believed that lymphogranulomatous adenitis was unknown in women (Hanschell, 1926), but it is now becoming recognized that typical inguinal poradenitis does occur, though inguinal bubonic manifestations are, on account of the different anatomical disposition of the lymphatic system in the female, comparatively rare; nevertheless, Galloway (1926) recorded his familiarity with typical inguinal buboes in Chinese and Japanese prostitutes in Singapore. Most of the cases of inguinal buboes in women who have given a positive intradermal test (*see below*) have been reported among prostitutes by French writers, though definite evidence of the infection of wife by husband has been obtained in an English case under the Editor's care.

Esthiomène and stricture of the rectum.—*Esthiomène* is an ulceration of the vulva associated with elephantiasis of the labia, formerly thought to be tuberculous. Stannus and others now believed that *esthiomène* is the counterpart of lymphogranuloma inguinale in the male. It has been recorded in all the countries of Europe and America, but there are very few references to it among tropical races, though Chesterman on the Congo found typical cases amongst the native women, and also saw the genito-ano-rectal syndrome there. Gray and Yieh, from Shanghai, described four cases in Chinese females. The primary lesion is probably hidden in the posterior wall of the vagina, and the ano-rectal lymphatic gland is the first to be attacked. The infiltration of this gland extends, *via* the lymph-flow, to the anterior part of the vulva, and posteriorly to the rectum, resulting in the *genito-ano-rectal syndrome*, and finally scarring of the glands leads to rectal stricture.

Fibrous stricture of the rectum, in both sexes, is probably due to the same virus. Authorities are now agreed that syphilis cannot be held responsible. Rectal stricture appears to be more frequent in Europeans than in native races, though Maxwell reported it comparatively frequently in China; Gray recorded it in both sexes in Nigeria, and Chesterman on the Congo. Rajam, in Madras, in a clinical study of lymphogranuloma and allied conditions, reviewed 183 cases of poradenitis, and found buboes in 99 males and 2 females, and the genito-anal syndrome in 18 males and 8 females. The virus spreads from the initial site of implantation by the lymphatics to the inguinal and pelvic glands, and later in the female the lymphatics of the anus and rectum become involved, producing at first proctitis and, later still, stricture of the rectum. In the male stricture of the rectum follows the occurrence of a primary lesion in the rectum. The following varieties are recognized :—

- (1) Anal stricture in women associated with *esthiomène*.
- (2) Annular rectal stricture.
- (8) Tubular rectal stricture.
- (4) Rectal communicating strictures from ulceration between the rectum, bladder, vagina, prostate and seminal vesicles.
- (5) This form of lymphogranuloma may be associated with carcinoma of the rectum. Rainey (1954) in 220 diagnosed as rectal stricture over a

period of 14 years found that in 5 the Frei test became negative by the time that carcinoma became apparent.

(6) In some cases it gives rise to a tender, fixed and palpable ileum resembling Crohn's disease.

In 1982 Frei reported that 80 per cent. of cases of the genito-ano-rectal syndrome gave a positive intradermal test.

Extra-genital infections.—Extra-genital infections have been recorded on the tongue, followed by glandular enlargements in the neck, by Curth; in the axilla by Hellerström; and on the foot by Lépinay and Grévin. A possible relationship with regional ileitis (Crohn's disease) was suggested by Likely and Lisa; they recorded a case in which multiple granulomata of the ileum were present with frank lymphogranuloma of vulva, vagina and rectum.

A few cases of meningo-encephalitis due to the virus of lymphogranuloma venereum have now been recorded.

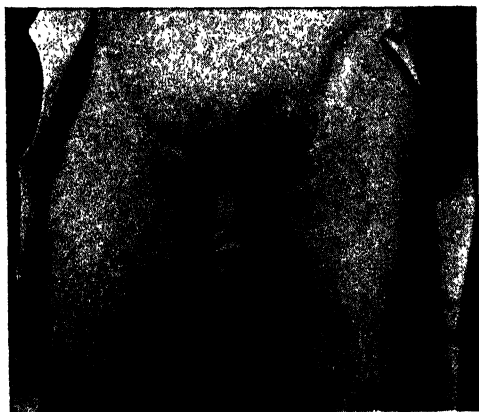


Fig. 137.—Climatic bubo two months after incision and circumcision, showing sinus formation.
(H. Wolfe Cowen.)

Ocular lymphogranuloma.—This was described by Macnie (1941). The whole globe may be covered with granulation tissue and the washings of the conjunctival sac will infect monkeys. Curth and Sanders found that a number of cases of uveitis and kerato-conjunctivitis simulating Parinaud's conjunctivitis gave positive intradermal tests; sometimes there is conjunctivitis with ciliary congestion. Fundus changes have been reported, also peripapillary oedema, dilatation and tortuosity of the veins.

Complications.—Sometimes, if too much lymphatic tissue is removed by excision of the glands, an elephantoid condition of the leg and scrotum on the affected side may develop (Fig. 137). This is a grave objection to surgical interference, added to the fact that secondary sepsis is very likely to ensue. Rupture of extensive lymphogranulomatous suppuration into the bladder has been recorded.

Diagnosis.—The diagnosis of climatic bubo and lymphogranuloma inguinale has been placed upon a scientific basis by the introduction of the intracuti-reaction (intradermal test) of Frei (1925), which is now known as the Frei-Hoffmann reaction. The antigen was originally prepared from the inflamed gland tissue.

Frei's original method of preparing antigen for the skin test consisted of withdrawing the pus from a gland which has undergone softening, but not fistulation. The aspirated pus is mixed with physiological saline, in the proportion of one part to five parts in a sterile tube, and immediately put up in 0.5 ml. to 1 ml. doses in Jena hard glass ampoules. Thus prepared, it is heated to 60° C. for two hours over a water bath, and the following day at 60° C. for one hour. The antigen should be preserved at a low temperature unexposed to light. Antigen can also be prepared from mouse brain or from the yolk sac of the developing chick embryo. Tests must be repeated every three months, and should give negative reactions in skin of normal and control patients suffering from *ulcus molle*. Careful experiments at the Albert Dock Hospital, London, with a controlled antigen prepared as above, have been satisfactory.

Ottolina (1941) claimed that intradermal injection of 0.3 ml. of cerebrospinal fluid from a previously proven case of lymphogranuloma gives a positive reaction. The cerebrospinal fluid is concentrated *in vacuo* from 10 ml. to 2 ml. before injection.

The Frei Hoffmann test.—The test is carried out on the same lines as the Dick or Schick sensitization tests: 0.1 ml. of antigen is administered intracutaneously in the forearm, causing a wheal 8–10 mm. in diameter. Physiological saline or *Dmelcos* chancroid antigen is administered on the other forearm as control. A positive result usually appears at the end of 24–48 hours and may vary in size from a circle of 1½ in. in diameter to a considerable reaction about 3 in. in diameter. German writers have noted a hard mass ("*Ein harter Knochen*") of infiltrated skin which may persist for a few days. This never occurs in negative cases.

The standard test of the Virus Reference Laboratory, London, supplies phials of Frei antigen each containing 0.15 ml. of infected yolk sac and each phial of control material 0.15 ml. of normal yolk sac. One pair of phials suffices for one patient. 0.1 ml. of Frei antigen is injected intradermally into the left forearm and 0.1 ml. of control material intradermally into the right forearm. A positive reaction consists of a papule on the left arm, at least 7 mm. in diameter reaching its maximum in about 48 hours. If any reaction to the control material in the right arm also occurs the test must be regarded as negative or doubtful.

In *biopsy* specimens the essential lesion consists of little pin-point epithelioid formations scattered throughout the lymphatic gland and giant cells are commonly seen. A greater proportion of cases can be diagnosed by this method than by the intradermal tests.

The Wassen test consists of producing a fatal encephalitis in mice by inoculation of the virus.

It should be noted that a positive intradermal test may be obtained in trachoma, ornithosis and psittacosis and virus pneumonitis.

The disease must be differentiated from soft sore, filarial adenitis, and plague, especially the ambulant form. In China, especially, lymphogranuloma buboes have to be distinguished from *pestis minor*; they have also to be differentiated from femoral hernia, but these two conditions may be associated. Tularemia may also have to be differentiated.

Blood changes.—There is usually a leucocytosis accompanying the suppuration. In the Editor's cases this has invariably been so; the

leucocyte counts vary from 8,000 to 27,000, but no cell-type is particularly affected.

Serological changes.—Hyperglobulinæmia is constantly present. The total proteins are between 8.1 and 10.3 per cent. in florid cases. The serum albumin is about 3.9 per cent. ; serum globulin 3.9 to 5.6 per cent.

Combes (1945) found that 90.5 per cent. of his cases gave a positive formol-gel test and that there was a decided tendency to return to normal after a clinical cure. Therefore hyperglobulinæmia is of value in determining the activity of the disease.

A *complement-fixation* test has been described by McKee and his colleagues. The antigen, *lygranum* (M.L.), stored at freezing point, is made from infected lungs of mice ground up to make 10 per cent. suspension. The readings are taken at the end of thirty minutes at 37° C. The lowest initial dilution of serum is 1 in 2.

Here again other viruses of the lymphogranuloma venereum-psittacosis group may give a positive complement-fixation test. Tests with virucidal antibodies show, however, that the members of this group of viruses are not antigenically identical.

Treatment.—In the lymphogranulomatous stage the inflamed gland, if discrete, can be excised, and the spread of further mischief appears to be avoided, but surgical interference to lay open the suppurating sinus or remove large masses of lymphatic tissue should be strongly deprecated for, as a result, the gland tissue may become secondarily infected with pyogenic organisms, a permanent lymphatic sinus may form, or chronic lymphatic obstruction may ensue. Usually, excision of the mass when suppuration is present is not followed by clean and rapid healing, but by the formation of sinuses (Fig. 137). Stammers and Law found that surgical removal of the originally infected "feeding gland" may lead to the subsidence of a larger group of secondarily involved glands.

Treatment by drugs.—*Sulphonamides.*—MacCallum and Findlay, by means of chemotherapeutic experiments on the virus of lymphogranuloma in the mouse, have shown that sulphonamides have a definite value. At present it is impossible to say why viruses of the lymphogranuloma venereum-psittacosis group are alone susceptible to sulphonamide action, while so many other viruses are insusceptible, but the evidence so far obtained seems to point to the fact that living virus may still be obtained from the brains of certain mice after prolonged treatment with sulphonamides.

In the treatment of the disease in man Montel (1937), in Indo-China, found the French preparation, rubiazol, curative, if given in courses over a prolonged period. Earle (1939) reported on the value of sulphapyridine, but recent reports indicate that in actual practice the results are disappointing.

The best two drugs are sulphathiazole and sulphadiazine. In early cases 6 grm. should be given on the first day of treatment, followed by 3 grm. daily for 20 days (a total of 66 grm.). Sulphonamides have also given remarkable results in cases of conjunctivitis due to lymphogranuloma venereum virus.

Aureomycin.—Greenblatt (1950) states that lymphogranuloma does not respond to penicillin or streptomycin, but that aureomycin appears to be more effective in the later, rather than the earlier, stages. Sinuses, proctitis, and inflammatory strictures show marked improvement when 70–100 grm. are given over 37–60 days, but ulcers show poor response. Chloromycetin is not nearly so good.

Alergant (1950) gives 250 mgm. per mouth every six hours to a total of 7 grm. Robinson and colleagues (1950) gave intramuscular injections in amounts from 0.56-3.6 grm., but these were painful. Proctitis shows great improvement. The complement fixation test is unsatisfactory as an index of therapeutic effect.

Terramycin (oxytetracycline) has been given by Maynard in doses of 15-36 grm. in a period of 15-30 days with success. Erythromycin, 200 mgm. four times daily for 8 days has not been so satisfactory.

Treatment of rectal stricture.—The treatment of rectal stricture is difficult. Palliative measures consist in dilating by graduated bougies and injecting antiseptic solutions to cure the ulceration. Operative measures depend entirely upon the type of stricture present; Lockhart-Mummery gave the following alternatives: internal proctotomy; complete proctotomy; excision of the stricture or of the rectum; and colostomy. Bensaude and Lambling, on the other hand, consider diathermic dilatation to be the best method, applied for twenty minutes every two or three days, for ten to twelve applications. Oil-soluble local anæsthetics, such as proctocaine, are best for post-operative rectal pain.

The medical treatment of rectal stricture and esthiomène has been improved by the introduction of sulphonamides. Shropshear claimed success with sulphapyridine, in doses of 2 grm. daily, for fifteen days, with a seven- to ten-day interval, after which the course is repeated. Two patients required 108 grm. in two fifteen-day treatments before symptoms disappeared. In women sulphapyridine checks leucorrhœa and heals the ulcers. Sulphadiazine, if continued over long periods of six months to a year, has given remarkable results. One method is to give the sulphonamide for 10-12 days every month. Aureomycin also is undoubtedly of value.

CAT-SCRATCH DISEASE

In 1932 Lee Foshay in Cincinnati discovered this curious disorder whilst investigating tularæmia. The ætiological agent is a virus of the lymphogranuloma-psittacosis group and has been transmitted to human volunteers and to monkeys. It has now been found in France, America and in Great Britain. The primary lesions consist of a general infiltration of the corium by lymphocytes, polymorphs, plasma and eosinophils.

The clinical picture is of non-fatal systemic illness. There is always a history of contact with cats. The primary lesion is followed 7-21 days subsequently by regional adenitis.

A positive intradermal test (Mollaret) is generally accepted as a reliable indication of active or previous infection (Brand and Finkel, 1956). It produces a wheal 1 cm. in diameter in 48 hours. The antigen is derived from pus or from infected lymph glands. Hinden (1957) has described five examples, four in children, with lesions in the axilla and in groin. One had conjunctivitis and preauricular adenitis. Cat-scratch disease may simulate a wide variety of lymph-node lesions, such as tularæmia, infectious mononucleosis, Hodgkin's disease, tubercular adenitis, lymphogranuloma venereum and both benign and malignant disease. The glands in the axillæ may reach the size of a tangerine.

The pathological changes consist of a marked reticulo-endothelial proliferation in the lymph nodes which may undergo central necrosis.

Complications so far recorded include a mild encephalitis and pneumonia (Sheldon and Smellie, 1957). Sequelæ of cat-scratch disease consist of erythema nodosum and transient generalized rashes. (A very complete account is given by H. Ruge (1954) in *Zentbl. f. Haut. Geschlechtskn.*, v. 87, 4/5, 177).

CHAPTER XLI

ULCERATING GRANULOMA OF THE PUDENDA

Synonyms.—Granuloma Venereum, Granuloma Inguinale; Donovanosis.

Definition.—An infective and granulomatous condition of the pudenda, widespread in some parts of the tropics, conveyed by sexual contact and auto-inoculation.

Geographical distribution.—Ulcerating granuloma is widely diffused in India, Guiana, Brazil, West Indies, Porto Rico, Papua, Pacific islands, and Northern Australia; sporadically it occurs in the Southern United States, on the West Coast of Africa, and in Southern China. De Vogel relates that in the southern region of Dutch New Guinea this disease appears in epidemic form and threatens the extinction of the local tribes. In only one case has spontaneous cure been observed. A few cases have been found outside the tropics. One is described from Scotland by Fergusson and Roberts (1953).

Ætiology.—There is good reason for believing that the disease is generally, though not invariably, venereal; very rarely, extragenital lesions have been observed. Cleland and Strangman in Australia, Flu in Surinam, and Aragão in Brazil described certain parasitic bodies within the large mononuclear cells from scrapings of the lesions. The organism is like a short bacillus with rounded ends, and measures $1\ \mu$ by $0.2\ \mu$; it was described and named *Calymmatobacterium granulomatis* by Donovan, and later by Araujo. It is now known as a bacterium: *Klebsiella inguinale* allied to *B. mucosus capsulatus*. It is termed in U.S.A. *Donovania granulomatis* and can be grown at 37° C. in the yolk sac of chick embryo only (Dunham and others). The secondary invader may be the non-hæmolytic anaerobic streptococcus described by Meleney (p. 642).

Dienst and Greenblatt (1943) have not confirmed previous observations, and now think that the Donovan bodies are protozoa, in no way related to bacteria (the diphtheria group) and have confirmed its true ætiology by reproducing the disease in negro volunteers (1939). The organism is selective for its particular host, reproduces by multiple segmentation within endothelial cells and is affected by antimony. The bodies are further distinguished by retaining basic fuchsin stain, when exposed to weak decolourizing agents. The smear from an ulcer is fixed, flooded with 0.5 per cent. aqueous fuchsin for two minutes, then washed with water and 0.5 per cent. citric acid until the dye ceases to leave the smear (5 sec.). The film is then washed in water and counterstained with 1 per cent. aqueous aniline blue for 5 minutes. Donovan bodies, when stained by hæmatoxylin and silver salts, have a closed "safety pin" appearance because of the ovoid shape and dense bipolar staining. A positive intradermal reaction with triturated infected yolk sac as antigen containing Donovan bodies has been demonstrated by Dienst (1947).

Age and sex.—Ulcerating granuloma has not been recorded before puberty; it has been found only after the age of 18 or 14, and up to 40 or 50. It occurs in both sexes, but more often in women, especially where polyandry is practised. Transmission by *Phthirus pubis* is suggested by Butts and Olansky (1946).

Pathology.—Histologically this disease is allied to rhinoscleroma, and

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the close association between these two diseases in Sumatra has been emphasized by Snijders. It is a reticulo-endotheliosis and on microscopical examination the new growth at the margins of the sores is found to be made up of nodules, or masses of nodules, consisting of round cells having large and, usually, badly-staining nuclei. These cell-nests of Malpighian cells are embedded in a delicate fibrous reticulum. The predominating cells are the plasma and endothelial cells forming small polymorphonuclear micro-abscesses described by Allen (1948). An important feature in the histopathology is a peculiar pathognomonic cell described by Pund and Greenblatt (Fig. 138). It is a large mononuclear varying from 25 to 90 μ in diameter, probably derived from a plasma cell. The specific cell, laden with the so-called Donovan bodies, can be shown best by the *Dieterle silver impregnation* method in which these bodies appear as dark brown or black elongated ovoid masses with intense bipolar staining. The nodular masses are, for the most part, covered by epithelium, their under-surfaces



Fig. 138.—Ulcerating granuloma of pudenda showing the pathognomonic cell and contained Donovan bodies. (After Pund and Greenblatt, "Archives of Pathology.")

merging gradually into a thick, dense, fibrous stroma in which small clusters of similar round cells are here and there embedded. The growths, though very vascular, contain no hæmorrhages; and there are no signs of suppuration or of caseation, no giant cells, and no tubercle bacilli. In vertical section of the small nodules the round-cell mass will be found to be wedge-shaped, the base of the wedge being towards the surface; the deep-lying apex is usually pierced by a hair or two. The growth is found around sebaceous follicles, blood-vessels, lymphatics, and sudoriferous glands; but it is especially abundant, and most deeply situated, around hair follicles.

Symptoms.—The incubation period appears to be comparatively short, from two to eight days after sexual contact, but it may be as long as twelve weeks. The disease commences in the great majority of cases somewhere on the genitals, usually on the penis or labia minora, the pubes, or groin, as an insignificant, circumscribed, nodular thickening and elevation of the skin. The affected area, which on the whole is elevated above the surrounding healthy skin, and covered with a very delicate, pinkish, easily-rubbed-off epithelium, excoriates readily, exposing a surface which tends to bleed and break down, although rarely ulcerating deeply. The disease advances in two ways: by continuous eccentric peripheral extension, and by auto-infection of an opposing surface. It exhibits a distinct predilection for warm and moist surfaces, particularly the folds between the scrotum and thighs, the labia, and the flexures of the thighs (Fig. 139).

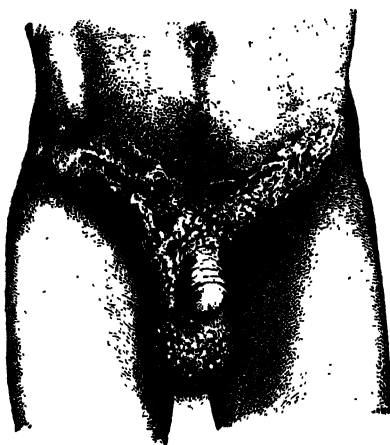


Fig. 139.—Ulcerating granuloma of pudenda in male.

Its extension is very slow, years elapsing before it covers a large area. Concurrently with peripheral extension, a dense, contracting, uneven,

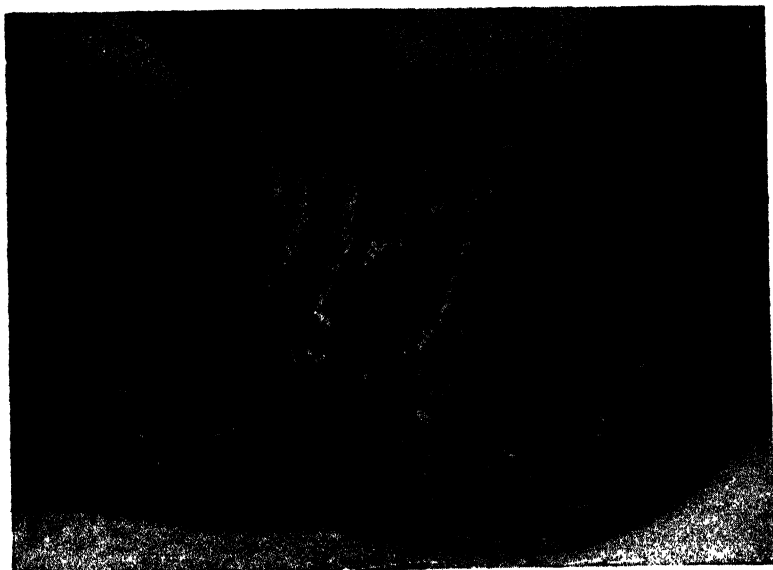


Fig. 140.—Ulcerating granuloma of pudenda in female. Australian aborigine. (Dr. H. Basedow, Adelaide.)

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readily breaking down scar forms on the surface travelled over by the coarsely or finely nodulated elevated new growth which constitutes the peripheral part of the diseased area. Occasionally, islands of active disease spring up in this scar tissue; but it is at the margin of the implicated patch that the special features of the affection are best observed. In cases of long standing the partially-healed areas are covered with thin depigmented skin and thus show up as white patches.

In the female (Fig. 140) the disease primarily attacks the crura of the clitoris, thence extending into the vagina, over the labia, and along the



Fig. 141.—Ulcerating granuloma of face and penis in a Chinaman. (Dr. B. Hawes.)

flexures of the thighs. The women thus affected are rendered sterile. In the male the disease may spread over the penis, involve the glans, scrotum, and upper part of the thighs (Fig. 141). Occasionally, the glans penis is not involved. In either sex it may spread in the course of years to the pubes, over the perineum, and into the rectum, the recto-vaginal septum in the female ultimately breaking down. At times, a profuse watery discharge exudes, and even drips from the surface of the new growth, soiling the clothes, soddening the skin, and emitting a peculiarly offensive odour. In this condition the disease, slowly extending, continues for years, giving rise to inconvenience, and perhaps seriously implicating the urethra, vagina, or anus, but not otherwise materially impairing the health. In neither sex do the lymphatic glands become affected. The disease continues entirely local, but in the process of cicatrization the lymph-channels may become blocked, and pseudo-elephantiasis of the genitalia may occur. Impassable strictures of the urethra may result, and recto-vaginal fistulae are common. It may even cause

death by eating its way into the bladder, causing septic cystitis, as in a long-standing case under the Editor's care.¹

An interesting development has come to light of the existence of metastatic deposits in this disease. Thierfelder and Thierfelder-Thillot in 1924 recognized metastases in nose, middle ear, mastoid process, mandible, forehead and liver in a case of gross granuloma venereum of the pudenda. These were also described by Rajan and Ranjah, Mathur and Dutta in 1953 in a case of a 13 year old girl in the Punjab. The disease spread from the cervix to the bladder, causing a vesico-vaginal fistula and subsequently metastases were found in bone and liver

¹Bowesman has described keloid formation which is so apt to occur in the healing scars, especially in Africans.

from which the Donovan parasites were recovered. Metastases in the liver have also been described by Bhatia in Madras.

Diagnosis.—Malignant and syphilitic ulcerations of the groin are common enough; the disease under notice, however, differs widely from these—clinically, histologically, and therapeutically. It is characterized by extreme chronicity—ten or more years; by absence of cachexia or of any tendency to cause death; by non-implication of the lymphatic system as a whole, and by non-amenability to mercury and iodide of potassium.

The disease which it most resembles is lupus vulgaris. From this it differs inasmuch as it is practically confined to the pudendal region; tends to follow in its extension the folds of the skin; and is not associated with the tubercle bacillus, giant cells, caseation, or other evidences of tuberculous disease. Unless complicated by a coincident syphilitic infection, the Wassermann reaction is negative. The inefficiency of antisyphilitic treatment soon convinces the physician that the ulceration is not due to this disease. Its characteristic mode of spread suffices to distinguish it from epithelioma and carcinoma. The discharges from ulcerating granuloma have, moreover, a peculiar acrid smell. Pund and Greenblatt described a fungating form affecting the cervix uteri in negroes, which greatly resembles the ulcerative and vegetative type of carcinoma of the cervix. It has also to be distinguished from gonorrhoeal endocervicitis and from simple erosions. The characteristic cells (plasma cells, etc.) may be demonstrated by biopsy.

Treatment.—Scraping and caustics, including the actual cautery, have been freely employed; but, although some improvement may be effected, new nodules almost invariably spring up in the resulting cicatrix. Complete excision, where practicable, offers the best chance of permanent cure; such a proceeding has to be undertaken before large areas and important passages have become involved.

Treatment by intravenous injections of tartar emetic, introduced by Aragão and Vianna in 1913, has proved successful, although in a small proportion of cases relapses occur. The drug should be injected on alternate days, commencing with $\frac{1}{2}$ gr. dissolved in distilled water and gradually increasing by the same amount up to the maximum individual dose of 2 gr., but the total amount required to effect cure varies within wide limits. Cicatrization usually takes place rapidly, but indolent ulceration may persist. Stibacetin, neostibosan, and other pentavalent compounds of antimony are more efficacious than tartar emetic, in total dosage of from 3 to 4 grm. Giglioli, in British Guiana, gave two courses of seven intravenous injections with 45 days between each course. Each consisted of 0.1–0.6 gm. of stibacetin dissolved in 20 ml. of normal saline, and this drug was successful in cases resistant to tartar emetic. Anthiomaline, as in lymphogranuloma, has also been used with success. The Editor has found it advisable to dress the open granulations daily with an ointment containing 1 per cent.¹ of antimony tartrate in white vaseline. It should be left on for two hours, then wiped off carefully, and the sore washed with boracic solution and dressed with boracic ointment. Radiant heat applied to the ulceration has proved beneficial, while touching indolent spots with a silver-nitrate stick will sometimes promote healing. Tartar-emetic treatment may be combined with X-ray and with protein-

¹ To make antimony-tartrate ointment the necessary amount of antimony tartrate is first dissolved in a small quantity of liquid paraffin and then made up to strength with white Vaseline. The ointment must not be spread on the healthy skin.

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shock treatment (Hanschell). These should alternate with tartar emetic injections. Operative measures, such as the amputation of a badly ulcerated glans penis, may become necessary.

In addition to medicinal means, it is often necessary to open up sinuses and to cauterize undermined margins by the electric cautery.

Many observers have drawn attention to types of ulcerating granuloma which are unaffected by antimony. Meleney drew attention to the curative action of *zinc peroxide* in the treatment of anaërobic organisms in acute surgical infections. The standard preparation is one which, when sterilized and suspended in distilled water, consistently yields oxygen while itself remaining soft. It must be rubbed into the wound, especially at its spreading margins, in gangrenous infections of the skin due to synergistic bacterial action, and in undermining burrowing ulcers of the non-gangrenous type. (Fig. 142).



Fig. 142.—Ulcerating granuloma of the pudenda infected with non-hæmolytic streptococcus. (Dr. Butterfield.)

To show healing with zinc peroxide treatment and extensive scar-tissue formation.

It is spread so as to come into contact with every part of the infected surface, particular care being taken to see that it penetrates the undermined skin and into the sinuses, for which purpose it is frequently necessary to use a short catheter. Strips of gauze or silk are dipped into the suspension, and introduced into the sinuses, but the dressings should be changed daily (Fig. 142). It may be found advantageous to syringe out the sinuses with hydrogen peroxide.

Sulphonamides, especially sulphapyridine, have been successfully employed. Ross and others recorded success with 8 gm. daily for fourteen days in early lesions. Earle regarded sulphonamides as useful adjuvants to antimony treatment.

Penicillin.—Turner (1945) has treated seven cases with penicillin which had proved resistant to antimony. It was given by intramuscular injection up to 4,000,000 units. The injections were given at intervals of 3–4 hours followed by local application of penicillin cream. Clinically all showed constitutional improvement. It was concluded that penicillin had no direct action upon the original disease, but cleared up secondary infections and thereby paved the way for further antimony treatment.

Streptomycin.—Greenblatt (1947) considered the success with this treatment remarkable. Fifty-eight patients were treated with 3·8–9·4 gm. of streptomycin, given intramuscularly in divided doses, four-hourly, to a total of 0·8–4 gm. per day. A course of 4 gm. daily for five days proved most adequate. Although lesions were still present, progressive healing still took place and was complete within one to three weeks. The results are far superior to those obtained with antimony. Toxic effects noted were cylinduria without renal involvement and some vestibular dysfunction. Recent experiences tend to show that dihydrostreptomycin is less toxic and equally effective.

Other antibiotics.—Robinson (1950) has stated that aureomycin, chloromycetin and streptomycin are all effective, but that the last-named remains the drug of choice. Greenblatt and others (1949) have reported especially good results with aureomycin by the mouth in 46 patients, some of whom had been resistant to streptomycin. The average dose was 20–30 gm. in 10–15 days. The smallest dosage was 10 gm. : the largest 70 gm.

Prophylaxis.—As this disease is most certainly spread by sexual connection, prevention consists in the avoidance of illicit intercourse, especially with native women.

Section VII.—TROPICAL SKIN DISEASES

CHAPTER XLII

NON-SPECIFIC, BACTERIAL, AND FUNGOUS SKIN DISEASES

I. NON-SPECIFIC SKIN DISEASES

LEUCODERMA

LEUCODERMA, or vitiligo, is extremely common throughout the tropics, and is by no means confined to any particular race. Almost any part of the body may be affected. The atrophied, unpigmented patches of skin slowly enlarge peripherally, and may coalesce. Occasionally the whole body is



Fig. 143.—Leucoderma. (Dr. H. K. Giffen.)

affected, and a certain amount of symmetry may be observed ; the hair of the affected parts may also become white (Fig. 143). The texture and glands of the skin remain normal. The ætiology of the disease is unknown.

Treatment.—*Bouchi* oil injections have for many years been employed by the Calcutta School of Tropical Medicine. The oil is extracted from the seeds of *Psoralea comyfolia*. Maplestone used it as an injection in conjunction with intestinal antiseptics. The oil is the same as that commonly used for external application. The dose is 0·05 to 0·1 ml. intradermally at the margins of the patch, and the number of injections varies according to its size. After two to three weeks formation of pigment is noticed and gradually spreads. A second or even a third series of injections may subsequently be given.

Sulzberger and Lerner (1958) have used the *psoralen* obtained from the plant *Ammi majus*. Extracts of this were employed in Egypt as an ancient folk remedy. Reports of the first scientific investigation of its photosensitising properties appeared in 1947 (Fahmy and Abu-Shady); there is no doubt that this substance applied topically or taken by mouth, *before the skin is exposed* to ultra-violet light will induce formation of pigment in some areas of vitiligo. Pigmentary response is obtainable only in those areas in which some melanocytes remain, but the incidence of severe inflammatory reactions to topical application of the psoralens is high; oral administration produces less dramatic side-effects such as nausea, diarrhoea and headache.

It is possible that cases with a positive Wassermann reaction are syphilitic and may be benefited by antisyphilitic treatment. Care must be taken not to mistake this condition for the depigmentation which is commonly seen in macular leprosy and yaws.

Leucoderma has to be differentiated from partial albinism. This is characterized by congenital absence of melanin. When the whole body is involved it is known as *universal albinism*. Albinism is usually inherited as a Mendelian recessive character, occurring more frequently in dark races. The affected areas are milky and superficial vessels are clearly seen. Involvement of the eyes is the chief danger.

CHELOID

Synonym.—Keloid.

Hypertrophic scars are common enough in Europeans consequent upon surgical scars or burns, but some Europeans are predisposed to develop the extensive hyperplasia known as cheloid. Central African negroes are especially liable, and in some tribes cheloidal scars on the back, thigh or chest constitute a readily recognizable tribal mark. Similar fibrosis may occur in these people after a cautery, a healed syphilitic chancre, or even mosquito-bites.

When fully developed, the growth is well defined; on a white skin it is pinkish or brownish, but it has a distinct red or chocolate tinge on a dark person. Growth takes place very slowly and, rarely, sarcomatous changes may supervene in the fibrous tissue. The growth may cause intense pain or a continuous ache when forming.

Treatment.—The most efficacious method, according to Macleod, is by radium. A full-strength radium plate is screened off by a silver sheet 1mm. in thickness. The exposure should last 18–30 hours. Less brilliant results are obtained by CO₂ snow, especially in early lesions. Electrolysis (3 ma.) is also useful, while occasionally X-rays are satisfactory.

Keloid ought not to be diagnosed as nodular leprosy, but the mistake has been made.

II. BACTERIAL SKIN DISEASES

ULCUS TROPICUM

Synonym.—Tropical Sloughing Phagedæna.

Geographical distribution.—Tropical ulcer is common in most tropical countries, particularly in those with a hot, damp climate, principally

in the jungle. These sores are often named after the regions in which they are specially prevalent—Mozambique ulcer, Yemen ulcer, Naga sore (Assam), etc.

Occasionally this disease assumes epidemic proportions. Lloyd Patterson described one such epidemic which "swept like a plague up the whole of Assam," seriously interfering with the efficiency of the labour force on the tea plantations.

This form of ulcer was very common among the carriers attached to the East African Force during the 1914-1918 war, and accounted for a considerable amount of invaliding, and among most Africans it causes an immense amount of disability. It is the commonest cause of disability amongst labourers in Malaya, the Solomon Islands, New Guinea, and indeed in the whole of Melanesia. The average stay in hospital may be 141 days in younger patients and up to 292 days in older ones, so intractable are these ulcers to treatment. In the West Indies, especially in Trinidad, and in India, the ulcers are rare in infancy, and Earle stated that they sometimes occur after the fifth year and attain their maximum incidence during the third decade. In a mixed community this incidence is highest in Indians. The majority occur during periods of low rainfall and low relative humidity.

Ætiology.—Prowazek attributed these ulcers to *Spirochæta schaudinni*, and these spirochætes are present, together with fusiform bacilli, in most ulcers.

Although sloughing phagedæna is evidently a germ disease, it is not readily communicated by ordinary inoculation either to man or to the lower animals. Apparently a concurrence of certain unknown conditions is essential. Lloyd Patterson, however, succeeded in producing a characteristic sore by bandaging a swab smeared with discharge from a typical lesion on to the surface of an abrasion, from which the scab had been removed, and this has recently been confirmed by Hare (1948).

Sloughing phagedæna is apt to attack the half-starved, malaria-stricken pioneers in jungle lands, over-driven labour gangs, and soldiers campaigning in the tropics. In such circumstances a slight wound, an abrasion, even an insect-bite, or an old chronic ulcer may serve as the starting-point for one of these terrible sores. Where yaws and sloughing phagedæna are co-endemic, the sores of the former may become infected with the virus of the latter, and serious sloughing and cicatricial contractions result. The feet and legs, being most exposed to injury, are the most frequent locations of this form of ulceration; but the arms, or any other part of the body, may also be attacked. The blood-calcium content, blood-sugar and blood-urea are said to be much diminished, probably as the result of deficient dietary (McCulloch). On the other hand, the Editor has observed several severe cases in otherwise healthy and well-fed Europeans in whom a dietetic deficiency could hardly be seriously considered.

Symptoms.—If the disease occurs in previously sound skin, the first indication is the formation of a larger or smaller bleb with sero-sanguinolent contents. The bleb may be attended with some pain and constitutional disturbance. When, in the course of a few hours, the bulla ruptures, an ash-grey, moist slough is exposed. The sloughing process rapidly extends in all directions until the skin and subcutaneous fascia over an area of one to many inches in diameter are converted into a yellowish, moist, horribly stinking slough. After a few days the centre of the slough begins to liquefy, the sore still continuing to extend at the periphery. In the course of a week or longer the sloughing process may cease and the slough be

gradually thrown off (Fig. 144). Then it is seen that not only have the skin and superficial fascia been destroyed, but in bad cases possibly muscles, tendons, nerves, vessels, and even the periosteum of the bones, have shared in the gangrenous process. Fortunately, in many instances, the deeper structures are spared, the disease being relatively limited and superficial. Sometimes, however, important structures, including joints, bones, and large blood-vessels, are destroyed; in such cases, even if life be spared, great deformity may ensue from different forms of ankylosis, or from strangulation of a distal part by a contracting cicatrix, necessitating amputation (Fig. 145).

Healed tropical ulcers leaving behind tissue-paper-like scars with pigmented edges are easily recognizable, and they constitute the familiar hall-marks of former prisoners of war in Japanese hands.



Fig. 144.—Ulcus tropicum.

Diagnosis has to be made from the ulceration of yaws, syphilis, amœbic ulceration of the skin, oriental sore, varicose ulcers, and veld sore, and is usually not very difficult, a final diagnosis being arrived at by exclusion.

Treatment.—As recent observations in Kenya Colony and Tanganyika Territory have shown that dietetics play an important part in the production of ulcus tropicum, it is of the first importance to correct any cachectic state. Thus, good food, fresh vegetables, lime-juice and chloroquine are almost invariably indicated. Corkhill in the Sudan found that much the same conditions hold there; cod-liver oil dressings, for instance, combined with a liberal vitamin A dietary give good results. Opium in full doses, not merely to assuage pain, but on account of its special action on the phagedænic process, is usually of great service.

Penicillin.—Since the routine use of penicillin in treatment the causative organisms are destroyed and the position has been transformed.

The action of penicillin is usually rapid and striking. Within 48 hours the discharge is reduced; the odour is mitigated and granulation tissue begins to form. If the ulcer is caught in the early formative stages, then simple dressings and rest will promote healing of a small one in a few days.

Penicillin is injected intramuscularly into the buttock. The most satisfactory preparation is Procain Penicillin G. suspended in oil with aluminum stearate (PAM) or the proprietary "Avloprocil" (I.C.I.). The dosage is 1 ml. (900,000 units) by intramuscular injection, repeated



Fig. 145.—*Ulcus tropicum* : acute case in a European, eventually causing loss

in 48 hours. This suffices to cure the majority of small ulcers. This stage also reacts to aureomycin in capsule form when given by the mouth:

(1) *Aureomycin* hydrochloride: 2 capsules (250 mgm.) 3 times daily for 2 days; or

(2) *Chloramphenicol* (chloromycetin): 2 capsules as above 3 times daily for 7 days.

(3) *Citrinin*: an antibiotic from *Penicillium thomii*, 0.5 grm. finely powdered, with bipotassium phosphate 0.87 grm. plus 100 ml. distilled water absorbed into gauze and applied to ulcer twice daily is advocated by Lejeune (1957).

The treatment of a chronic indolent tropical ulcer is a different story. Since the work of O'Brien (1951) it has been realized that the most satisfactory line of treatment is by occlusion-plaster (Poroplast, Scholl),

together with parenteral penicillin and skin grafting. Such treatment no longer entails admission to hospital as experience has shown that it can be carried out in the out-patients' departments and dispensaries. The patient is injected with PAM 1 ml. daily for 4 days prior to operation and for 1 week afterwards.

Hypertonic saline dressing should be applied to surface of sore three times daily. Sometimes it is advisable to apply a cream containing 500 units of penicillin per grm. All ulcers over 2 ins. in diameter, whether acute or chronic, are best treated in this way.

Preparation for grafting.—Saline dressings are applied and the surface is dusted with P.S.P. (penicillin, sulphathiazole and mag. carb. pond.) and covered with dry dressing. An amylocaine spinal anæsthetic, 2 ml. for an adult, suffices for the period of the operation (or intravenous pentothal).

The operation consists of complete excision of the ulcer area with a sharp scalpel, followed by Thiersch-grafting. All scar tissue must be removed and a smoothly sloping floor aimed at. A thigh tourniquet is placed in position and, before it is removed, a Thiersch graft is taken with an ordinary razor from the opposite thigh, is applied and grafts, 2 ins \times 3 ins. are readily cut. They should be fairly thin, just thin enough to leave a speckled surface of hair on the donor side. During this period the graft pieces must be kept in sterile saline solution. As soon as the ulcer is completely covered by the grafts, a bland dressing with petroleum jelly is applied, then a layer of lint and a pad of cotton wool.

The application of a crêpe bandage to the dressing overlying the graft must be accurately and firmly done. It is important that it should be left in position for one week. At the first examination after the expiry of the week, penicillin in oil dressing is applied and renewed whenever necessary. It is reported that the grafts "take" in 90 per cent. of cases and that healing is complete within three weeks.

The knife specially adapted for the operation is a large curved *bistoury* (curved on the flat in addition to the normal curve).

According to Enzer and other observers, when the Thiersch method fails, "pinch grafting" of small circular patches of whole skin, distributed over the area should be employed. In this case the grafts should be dressed with an emollient ointment, such as *Tulle gras Lumiere* (Anglo-French Drug Co., 288 Gray's Inn Road, London, W.C.1).

In the after-treatment it is obvious that tropical ulcers will tend to recur unless the patient receives an adequately balanced diet; it should, of course, contain sufficient animal protein whilst green vegetables and fruit will ensure an adequate supply of vitamins A and B₂ complexes.

Excision knife for tropical ulcer.—Manuwa's excision knife (Down Bros.) Bistoury, with a curve on the sharp side and a curve on the flat to enable it to fit the edge and concavity of the ulcers is recommended.

The method is to apply the edge of the knife to the skin 3 mm. ($\frac{1}{8}$ in.) beyond the edge of the ulcer, and with a sawing motion, slice off the ulcer almost an $\frac{1}{2}$ in. deep to the surface, emerging the same distance on the opposite side. This

leaves a clean, slightly concave bed, which can be immediately grafted. The excision takes only a few seconds.

This knife is made in three sizes.

VELD SORE

Synonyms.—Septic Sore; Desert Sore; Barcoo Rot.

Geographical distribution.—This peculiar ulceration is widely distributed in the tropics and subtropics wherever desert conditions exist. It has long been known in Queensland and the Northern Territory of Australia. It affected the British troops in the Sudan and South African campaign 1900–1902, and caused a very considerable amount of disability in Gallipoli, Egypt, Palestine and Iraq during the 1914–18 war. It was also prevalent in British troops in Palestine, Libya, Abyssinia, Eritrea and the Middle East during the 1939–1945 war. In South Africa it is familiar to sportsmen and travellers.

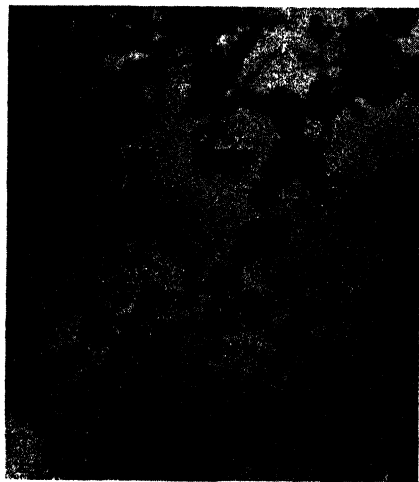


Fig. 146.—Culture of Klebs-Löffler bacillus obtained from the veld sore shown in Fig. 147. (Dr. H. K. Giffen, Assiut, Egypt.)

Ætiology.—The cause of this condition had long been obscure. H. H. Scott (personal communication) isolated the diphtheria bacillus from a veld sore in the S. African war in 1901, and succeeded in curing it by application of anti-diphtheritic serum. In 1916 Craig, in the Sinai Desert, demonstrated the diphtheria bacillus in the lesions. Whether this covers the ætiology of all veld

sores cannot at present be affirmed, but that a certain proportion are diphtherial in origin may be taken as established. By sterilizing the surface of the sore with absolute alcohol and scraping the clear surface, a culture of the Klebs-Löffler bacillus could be obtained on Löffler's serum. This organism was pathogenic to guinea-pigs and quails, and its lethal effects could be neutralized by injection of anti-diphtheric serum. In the serous contents of the blebs the typical granular bacillus was observed in stained preparations. (Fig. 146.)

The desert sores, as the Editor observed them among British troops, occurred most frequently in men of mounted units, especially those associated with horses and camels, and in the 1939–1945 war similar lesions have also been seen in cavalrymen. The rate of incidence coincided with that of a widespread epidemic of faucial diphtheria. Cameron and Muir (1942) described the lesions as they occurred in mounted units in Palestine. Acute and chronic stages were recognized. Paralyses occurred in a number of patients in whom there was no other focus of infection than the skin. Not all sores on exposed parts are necessarily diphtherial in origin; some are primarily staphylococcal. In Eritrea and Abyssinia it was noted by Louw that the men of mechanical units with oil or grease on their clothing suffered less than others from septic ulceration. Excessive dryness of the skin is a predisposing factor.

Symptoms.—The sores occur almost invariably on the exposed parts, mainly those covered by hairs, such as the dorsum of the hand, the fore-arm, the elbows and knee-joints. Sometimes the lesions occur on the face, over the eyebrows and on the cheeks. They may arise *de novo*, or be superimposed on some abrasion.

A regular sequence of events precedes the actual ulceration. At first a *vesicle* full of straw-coloured fluid makes its appearance, generally in the vicinity of a hair follicle; it may vary considerably in size. The pain it occasions is quite out of proportion to the size of the lesion. On bursting it leaves behind a shallow *ulcer* covered with a thin grey pellicle. The raw ulcerated surface is exquisitely tender, and it may continue to spread peripherally. (Figs. 147, 148.)

After the inflammatory changes have lasted two or three weeks the ulcers enter upon a *chronic stage*. Then they are characteristic in appearance and perhaps are more familiar to practitioners than in the incipient stages. The ulcers are punched-out, circular, with undermined edges and thickened margins; their base is covered with grey-coloured and scaly débris, beneath which



Fig. 147.—Veld sore on leg containing growth of Klebs-Löffler bacillus.
(Dr. H. K. Giffen.)

can frequently be distinguished an adherent membrane, but little or no pus is discharged. The peculiar ulceration which results is most intractable, and resists all external forms of medication; the edges become indurated, and the thickened tissue has a cyanotic appearance. In sores in which healing does take place, a thin paper-like scar remains for several years. The actual ulceration may continue for two years or longer.

The Klebs-Löffler bacillus can be isolated from the primary lesions; from the chronic ulcerations it is recovered with difficulty, being overgrown with staphylococci and other organisms of suppuration. The best medium is Marshall's tellurite.

Diphtheritic pareses, or paralyses, have been observed in association with these sores; in one series this complication occurred in 27 per cent. Paralysis of the palate, arms and legs, and accommodation paralysis of the iris have been recorded. There may be ataxia, loss of knee-jerks, anaesthesia and incoordination, recalling at first sight locomotor ataxia or beriberi. Walshe pointed out that the initial local paresis is in anatomical relation to the site of the infective focus, and may be taken to indicate direct passage of toxins from the diphtheritic lesion along the neural channels to the central nervous system. Accommodation

pareses, on the other hand, usually appear in the second week, no matter what the site of the local lesion may have been. Polyneuritis is usually delayed for three weeks or longer.

Ward and Mason (1945) have described similar cases during the Burma campaign. The first symptom of nervous involvement was blurring of vision, tingling, numbness and coldness of extremities. On examination there was asteriognosis and ataxia.

Treatment.—The specific treatment for this kind of ulceration is antidyphtheritic serum, which has a very striking effect in healing up ulcers that have persisted for a year or even longer. At least 20,000 units should be given, and should be injected subcutaneously or intramuscularly in the vicinity of the sores. Sulphonamides by the mouth have been found useless, but in chronic

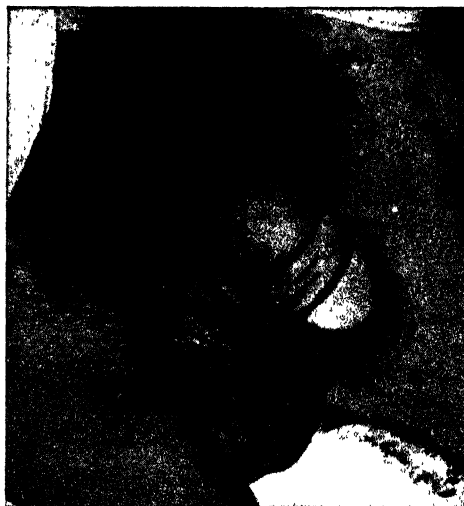


Fig. 148.—Veld sore. Primary lesion on adductor aspect of thigh; secondary contact sore on scrotum. (Capt. Manton.)

cases staphylococcal vaccines are advocated, together with compresses of hypertonic saline, cod-liver oil dressings, and elastoplast bandages. In some cases silver nitrate stick is beneficial. Saline solutions of penicillin applied to sores accelerate healing.

In staphylococcal sores sulphonamide paste and acriflavine ointment have been employed (acriflavine, 0.1 per cent.; adeps lanae anhydrous 45 per cent.; water 100 per cent., to which is added 10 per cent. *sodi sulph.* for osmotic effect). Penicillin in full doses should be used.

Prophylaxis.—Protection of exposed parts of the body, especially the knees, against abrasion in desert regions where these sores occur, is obviously indicated. Mounted men should wear knee-breeches and should not be permitted to ride in shorts. The application of antiseptic lotions to any abraded surface at the earliest possible moment is also indicated. As there is some evidence that dried horse-manure may act as a nidus of the bacillus, care should be taken to avoid contact with this as far as possible.

SEBORRHOEA (O'DONOVAN AND MICHAELSON, 1946)

Lesions of the face or scalp, especially those of seborrhoeic nature, are associated in some with kerato-conjunctivitis which appears to be identical with that described as epidemic virus kerato-conjunctivitis, and is allied to herpes simplex. It is associated also with seborrhoeic dermatitis. The onset of the skin lesion precedes that of the ocular by a definite short interval of time.

III. PARASITIC DERMATITIS

CERCARIAL DERMATITIS (SCHISTOSOME DERMATITIS)

Cort in Michigan (U.S.A.) in 1928 drew attention to a special kind of dermatitis produced by *Cercaria elvæ*, and *C. douthitti* was soon afterwards found to cause similar lesions. In England and Wales dermatitis after bathing in ponds and reservoirs has been noted by Matheson, Taylor and Baylis as due to *C. ocellata*, a form closely allied to *C. elvæ*. The cercariæ burrow in the skin, where their heads become arrested and cause a pustular eruption. All these cercariæ are derived from different species of snails, especially *Lymnæa stagnatilis*. *C. elvæ* and *C. ocellata* are large cercariæ nearly 1 mm. in length overall, twice that of the schistosome cercariæ; the tail is bifurcated and all possess two suckers. Cercarial dermatitis is commonly known as "sedge-pool itch" or "swimmers' itch," and takes the form of an itching maculo-urticarial dermatitis, later becoming papular or pustular; it may be, after a few days, actually exanthematous. It is always connected with paddling or swimming in infected waters a few days previously. A somewhat similar dermatitis is noted in association with cercarial penetration in *Schistosoma hæmatobium* and *S. mansoni* infections.

"Sawah itch" in Malaya is caused by cercariæ of a cattle schistosome (Buckley). Paddy itch or "Koganbyo" is a lakeside disease in valleys adjacent to Lake Shingi, Japan, caused by cercariæ of *Gigantobilharzia sturniæ*. The intermediate host is a snail, *Polypylis hæmisphæcula*. The definitive hosts are starlings, sparrows and wagtails (Hunter and colleagues, 1951). Hunter has found two species of *Trichobilharzia* responsible for swimmers' itch in Seattle. The cercariæ can penetrate the skin of bathers. Fain in Ruanda-Urundi (Belgian Congo) found furcocercous cercariæ of the "ocellata" group which produced a similar condition and the species is *Cercaria herini* from the *Lymnæa undussumæ*. Cercarial dermatitis may occur even in salt water. Bearup has found a bifid tailed cercaria from the marine snail—*Pyragus australis*. Cases in seabathers have been recorded from California, Florida, Rhode Island, Hawaii and Australia.

IV. ALLERGIC AND TOXIC DERMATITIS

PYRETHRUM DERMATITIS

Pyrethrum dermatitis has been noted in Kenya, and is caused by the leaves and flowers of *Chrysanthemum cinerariæfolium*, which grows at altitudes of 500–7,000 feet and flowers throughout the year. The pyrethrum content is 1–2 per cent. Absorption is facilitated by constant sweating, and exposure to sunlight greatly exacerbates the lesions. Some persons on contact exhibit merely a local dermatitis; others show a widespread allergy. Itching commences at the corner of the eyes, and is followed by lacrymation, an irritating vesicular rash, peeling of the skin, and formation of painful fissures.

POISON IVY DERMATITIS (DERMATITIS VENENATA)

Many tropical plants cause dermatitis which may assume an erythematous, vesicular or urticarial form. Intimate contact with the plants or its leaves is

necessary. Poison ivy (*Rhus toxicodendron* and *R. juglandifolia*) (Fig. 149), poison sumac (*R. vernix*), poison wood (*Metopium toxiferum*) in North Eastern and Southern United States cause intense dermatitis. Repeated attacks do not produce immunity. The venom is *toxicodendrol*. Treatment consists of washing the skin with soap and water; alcoholic or oily solutions must be avoided. Clothes must be decontaminated by immersion in 1 per cent. calcium hypochlorite for twenty minutes.

OTHER FORMS OF DERMATITIS

Several other plants and flowers may cause severe allergic dermatitis, such as *Cypripedium* (lady's slippers), *Euphorbia*, primroses, lilies and vanilla beans; sometimes also mangoes and, in Japan, lacquer made from *Rhus vernicifera*.



Fig. 149.—*Rhus juglandifolia* (Poison ivy). (Dr. L. A. León, Quito.)

Iroko dermatitis.—Idiosyncrasy to wood dust is not uncommon. Iroko is a trade name for *Chlorophora excelsa*, a tree of East and West tropical Africa, and known as African teak. The dust produces the usual signs of allergy, with skin irritation, edema of face, blepharospasm, acute coryza and pharyngitis. Other woods, such as satin wood, teak and mahogany, also produce allergy in susceptible persons. Obeche, or *Wa-Wa* (*Triplochiton scleroxylon*), a soft wood, produces similar symptoms.

V. CLIMATIC SKIN DISEASES

PRICKLY HEAT

Synonym.—Climatic hyperidrosis.

Prickly heat, or, as it is sometimes called, lichen tropicus, is probably a form of miliaria (not of lichen) connected with the excessive sweating incident to the heat of tropical climates in association with high humidity. It therefore occurs especially in the Red Sea, Persian Gulf, the plains of India, in Eritrea and Somaliland; in the New World, in Panama and in northern parts of South America. Europeans are specially liable; Africans are more or less immune.

Ætiology.—According to Pollitzer, the mechanism of its production depends on the non-cornification of the cells of the stratum corneum, the individual cells

of which, in consequence of being sodden by constant perspiration, swell, and so obstruct the orifices of the sweat-glands, thereby leading to accumulation of sweat in the ducts. The blebs and bullæ are due to breakdown of function in the second form of sweat glands of the skin, especially the large coil sweat glands localized to the axillæ and genital regions. The miliary rash, commonly known as prickly heat, is due to dysfunction of small sweat glands, and a pemphigoid condition due to dysfunction of the large sweat glands (apocrine), and it is often associated with heat exhaustion (see p. 386).

Small sweat glands (eccrine) are distributed over the skin, except that of the glans penis, margins of the lips and nail beds. They are more numerous on the palms than on any part of the body, except the soles. They average nearly 3,000 per sq. inch. Two-thirds of each gland is secretory. When the gland is at rest the cells are clearer and the nucleus is near the base of the cell, whereas after sweating, the cells become more granular and the nucleus is to be found towards the centre.

The large sweat glands are known as *apocrine glands* and are situated in axillæ, in the genital regions, around the anus (glands of Gay) and in the areola of the nipples. They differ in structure in that the coil is larger and may reach 3 mm. in diameter, and the tube which is correspondingly wider, tends to divide dichotomously into smaller tubules, which end in blind sacs in the subcutaneous tissues. Instead of opening on the surface the apocrine glands open with the hair follicle between the funnel and the mouth of the sebaceous gland, and they differ also in that they excrete part of their substance and the excretion has a characteristic smell. They are active during menstruation, pregnancy and have been described as cutaneous sex-glands.

Sweat has normally an acid reaction due to acid sodium phosphates but becomes alkaline in excessive sweating.

Miliaria profunda is associated with tropical anhidrotic asthenia. *M. chry-stallina* is a superficial, transient rash.

Symptoms.—Many Europeans in the tropics suffer from prickly heat, particularly during the earlier years of residence. Some never seem to become acclimatized, but continue year after year to exhibit their crop of prickly-heat lesions when the hot season comes round.

Though sufficiently annoying in the robust and healthy, prickly heat is not a grave affair. It is otherwise in the invalid, delicate sickly children, hysterical and, especially, parturient women; to these it may prove, by interfering with sleep and provoking restlessness, a very serious matter.

Prickly heat consists of a miliary-like eruption, *miliaria rubra*, generally most profuse on those parts of the body, as around the waist, which are closely covered with clothing; but it also occurs on the backs of the hands, on the arms, legs, forehead, occasionally on the face, the scalp, in fact on any part of the surface of the body except the palms and soles. The minute, shining, glass-like vesicles, and the numerous, closely-set, slightly inflamed papules, give the skin a feeling of being thickly sprinkled with grains of sand. The eruption may continue for months on end, becoming better or worse according to circumstances. The pricking and itching are often exceedingly distressing. Anything leading to perspiration immediately provokes an outburst of this almost intolerable itching—nothing more certain than a cup of hot tea or a plate of hot soup. As soon as the weather becomes cool the eruption and the irritation quickly subside. Horne and Mole (1949) made the interesting observation that prickly heat

is relieved by reducing salt intake and can be made to relapse by increasing the intake of table salt. These workers (1951) have found that raised sweat chloride and decreased conductivity of heat through the skin are present in cases of mammillaria, whether the anidrotic syndrome is present or not. The sweat chlorides begin to rise, whilst prickly heat is present before the mammillaria have become visible. Therefore a raised sweat chloride may be associated with severe prickly heat. The reduction in sweating in areas of active prickly heat has been confirmed. Other forms of miliaria are *M. pustulosa* with numerous pustules unassociated with hair follicles. The purulent material is white and due to *Staphylococcus aureus*.

A very severe form consists of very painful symmetrical crops of blebs and bullæ in armpits and crutch. The bullæ are filled with thin pus, and are surrounded by a bright red ring of acute inflammation.

The pemphigoid state is a late stage of the disease, and is often complicated by secondary fungous infection.

Pathology.—O'Brien (1947), on histological studies, claims that a "civilized toilet" results in depriving the skin of its sebaceous secretions with the result that a keratin ring closes the orifices of the sweat ducts, so that a vesicle of sweat collects in the upper epidermis, causing a secondary reaction. The exuding sweat forms vesicles round the remains of the ducts and percolates downwards to the corium. If an area of skin is smeared with anhydrous lanoline this horny occlusion is prevented. With "lipoid response" plug-formation occurs beneath the vesicle and causes disintegration of the ducts with obstruction of the sweat flow and gives rise to a vesicular reaction deeper than that of prickly heat. This accounts for the persistent anhidrosis which follows and which may be associated with eczematous and exfoliative dermatitis. Sulzberger and his colleagues uphold the view that prickly heat and thermogenic anhidrosis are different manifestations of the same process.

Treatment.—Manifestly, the most important thing is the avoidance of all causes of perspiration—particularly the copious consumption of fluids, especially hot fluids—moderation in exercise, avoiding sea-bathing, close rooms, warm clothing, and so forth. A towel should be carried to mop up sweat. The sleeping-mattress and pillow should be covered with a finely woven grass mat, and the bed provided with what is known in the East as a "Dutch wife"—that is, a hollow cylinder, 4 ft. by 8 or 10 in., of open rattan work, over which the arms and legs can be thrown, and unnecessary apposition of sweating surfaces so avoided. A punkah at night is a great comfort. Biniodide of mercury, 1:1,000, with 1 oz. spirit (28.4 ml.), diluted with an equal quantity of water and menthol, 10 gr. (0.65 grm.), dabbed on the affected parts after bathing, and allowed to dry, is also recommended. Every bathroom in the tropics should be provided with some mildly astringent and antiseptic dusting powder. A very good one consists of equal parts of boric acid, oxide of zinc, and starch, such as Johnson and Johnson's anti-prickly heat powder. This should be freely applied, after careful drying of the skin, particularly to the axillæ, the crutch, under the mammæ in women, and between the folds of skin in fat children and adults.

As a prophylactic the frequent application of a salicylic-acid (1 dr.) and spirit (8 oz.) lotion has been advised. Pearse strongly recommended

the inunction of a mixture of almond oil and lanoline in the proportion of 8 to 1. Calamine lotion, with or without hydrocyanic, or carbolic acids (2 per cent.), relieves the itching. Inunction with lanoline or caladryl ointment is also recommended once a week. Loose-fitting "Aertex" garments of the bush-shirt type appear to be the best to wear. Relief from symptoms is produced by pyribenzamine, an anti-histamine preparation.

TROPICAL CHEIROPOMPHOLYX

This name is given to vesicular eruptions on the hands, fingers or feet usually known as dysidrosis. In the majority of cases these are due simply to eczema; others are signs of dermatitis due to external irritants, or are toxic eruptions due to ringworm infection of the toes. It is an example of interepithelial vesicular formation and is therefore similar to the eczema vesicle. Owing to the thickness of the horny layer on the hand, the vesicles cannot rupture as they would elsewhere, and remain in the skin for days like grains of boiled sago. The best treatment is calamine and lead lotion with liquor picis carbonis, and sometimes the addition of weekly doses of a quarter of a pastille of X-rays, not more than four in all.

It is claimed by Fitz-Patrick that a distinct form, endemic in tropical Africa and India, is caused by an anaërobic bacterium which attacks the palmar and interdigital aspects of the hands and the plantar aspects of the feet. A protective or pellanthum paste is soothing for the irritation. The following ointment is suitable :

Ichthyol	gr. 15
Zinc oxide	}	aa 3ss
Ol. oliv.		
Adeps. lanæ anhyd.	3i
Aq. calcis	ad 3ss

To be applied night and morning.

The ointment is rubbed well into the affected parts, and cotton gloves or socks are worn. In conjunction with this, resorcin soap should be used.

VI. FUNGOUS SKIN DISEASES

DHOBIE'S ITCH (TINEA CRURIS) AND PITTYRIASIS VERSICOLOR

Ætiology and nomenclature.—By the lay public all epiphytic skin diseases in the tropics—more especially all forms of intertrigo—are spoken of as *dhobie's* (washerman's) *itch*, in the belief, probably not very well founded, that they are contracted from clothes which have been contaminated at the washerman's. There are many sources of ringworm infection in warm climates besides the much-maligned dhobie.

In the tropics, native children often exhibit dry, scurfy patches of ringworm on the scalp; and the skin of the trunk and limbs of adults is not infrequently affected with red, slightly raised, itching rings, or segments of rings, of trichophyton infection. In some cases these rings enclose areas that are many inches in diameter.

Pityriasis versicolor (*Tinea versicolor*) is also very common in the tropics. It is the usual cause of the pale, fawn-coloured, slightly scurfy patches so frequently a feature of the dark-skinned bodies of natives. On the dark-pigmented skins of negroes, Indians and dark-complexioned Chinese, the patch of pityriasis—unlike that in Europeans and light-skinned Chinese—is usually paler than the healthy integument surrounding it. The pigment in the fungus and the profuse growth of the latter conceal, as a coat of paint might, the dark underlying natural pigment of the skin, which, moreover, in certain cases seems to be affected (either increased or decreased) by the action of the fungus. The disease is most commonly seen in young adults, is favoured by excessive perspiration, and especially by flannel underwear, and is rarely seen in the aged.



Fig. 150.—Dhubie's itch, symmetrical lesions in groins.

Several varieties of fungi may be involved in the production of pityriasis; besides *Malassezia furfur*, the best-known is *Cladosporium* (*Dematium*) *mansoni*, of which a culture in maltose-agar produces black hemispherical colonies, and correspondingly black patches on the affected skin. The mycelium and spores are refractile with slow budding. The *hyphæ* are 2–3 μ , the spores 3–8 μ . Fluorescence can be demonstrated in scaly patches by Wood's light.

The expression "dhubie's itch," although applied to any itching, ringworm-like affection of any part of the skin, most commonly refers to some form of epiphytic disease of the crutch or axilla. This infection has now become widespread in Great Britain and endemic in many English public schools, where it is spread by infected clothes and water-closet seats. The causative fungi are *Epidermophyton floccosum* (syn. *E. cruris*, *E. inguinale*, etc.), *Trichophyton mentagrophytes* (syn. *T. gypsum asteroides*, etc.), *T. rubrum* (syn. *T. purpureum*, *E. rubrum*, etc.) and *Nocardia minutissima* of erythrasma. *T. discoides*, the commonest cause of ringworm in cattle is occasionally transmitted to man.

E. floccosum is peculiar to man only ; it is easily cultivated, but grows slowly. On Sabouraud's agar medium it takes a week to develop, and appears first as a yellowish glabrous growth with a powdery surface in which masses of the characteristic pyriform spindles are found. Subcultures tend to be cottonous and show fewer spindles.

Symptoms.—The suffering to which certain forms of dhobie's itch give rise is often severe. In hot damp weather, especially, the germs proliferate actively, producing, it may be, smart dermatitis. The affection begins usually as slightly raised, rounded and elevated papules which spread peripherally, producing a raised festooned border covered with thick scales. The excessive irritation thus set up leads to scratching and, very likely, from secondary bacterial invasion, to boils or small abscesses. The crutch, scrotum or axillæ, are sometimes rendered so raw and tender that the patient may be unable to walk or even to dress (Fig. 150). It commonly extends backwards on the perineum and into the natal cleft about the anus. It often affects the skin under pendulous breasts and occasionally forms patches resembling tinea circinata on the thighs. The irritations thus produced are usually worse at night, and may keep the patient awake for hours. Even without treatment, when the cold season comes round, the dermatitis and irritation subside spontaneously. The affected parts then become dry, pigmented, and scurfy, and the fungus remains quiescent until the return of the next hot weather.

Diagnosis.—The diagnosis of mycotic dermatitis is usually easily made, the festooned margin is almost conclusive. If doubt exists, the microscope may be necessary ; but, owing to the inflamed condition of the parts, there may be much difficulty in finding fungous elements, even when the case is certainly epiphytic. A negative result is, therefore, not always conclusive against ringworm. The mycelial elements can be distinguished in epidermal scales soaked in liquor potassæ. It has to be distinguished from *seborrhæic dermatitis*, *intertrigo*, *flexural psoriasis* and *dhobie mark dermatitis*.

Treatment.—The patient should get two pairs of running shorts, which should be worn on alternate days, the pair not in use being boiled. After a thorough use of soap and water, a preliminary soothing treatment by lead lotion, or an ichthyol or hazeline cream, is desirable.

Chrysophanic acid may be prescribed in the following form with gutta-percha, and should be painted on with a brush on alternate nights.

Acid. chrysophan.	.	.	.	gr.xx	(1·296 grm.)
Chlorof.	.	.	.	ʒi	(3·5 ml.)
Liq. gutta-perchæ	.	.	.	ʒi	(28·42 ml.)

Cignolin is a synthetic chrysarobin and is useful in all fungoid skin affections. Cignolin is apparently free from toxic action on the kidneys, and in neat concentrations it can be applied to the scalp without any danger of conjunctivitis. The prescription is cadojel (a proprietary tar preparation), 1 grm. ; cignolin, 0·1–0·2 grm. ; benzol, 10 grm. If cadojel is not obtainable, a suitable formula is :

Ol. cadini (deod.)	.	.	.	℥xl	(2·368 ml.)
Cignolin	.	.	.	gr.iv	(0·259 grm.)
Benzol. rect.	.	.	.	ʒi	(28·42 ml.)

The method of application is very simple, the affected areas being painted with the solution twice daily and then covered with strips of gauze. If there is too much irritation, then the painted areas are further protected with a thin layer of Lassar's paste or calamine lotion.

The patient should be isolated and kept in clean pyjamas during treatment. For three days cignolin, 2 per cent. in soft paraffin, is applied with bandages.

For those who cannot tolerate cignolin "Mycozol" is suitable and consists of :

Acid. salicyl.	4 per cent
Chloretone	5 "
Mercury salicylate	4 "

in a mixture of lanoline and soft paraffin.

Grisovin (Griseofulvin) Glaxo: *Fulcin* (I.C.I.).—The oral fungicide which offers a new approach in treatment should be given in doses of 1·5 grm. daily for adults for 2–4 months. For children half this dose is appropriate. Brian Russell and colleagues have obtained strikingly successful results, especially in chronic infections. Clinical improvement can be expected in eight weeks and the skin is normal by the sixteenth.

In America undecylenic and propionic acids have been found effective in all forms of tinea infections. Undecylenic acid is used in the form of 10 per cent. to 20 per cent. cream of the carbowax or lanette wax types; a dusting powder containing 2 per cent. undecylenic acid and 20 per cent. zinc undecylenate is also employed. Mixtures containing them are also effective :

Undecylenic acid	.	.	5 per cent.
Zinc undecylenate	.	.	20 "
Vanishing emulsion base up to			100 "

For the ringworms of the thick-skinned natives, linimentum iodi of double strength, freely applied, is the best, speediest and most efficient remedy, but it is too irritating and painful for the European skin.

Prophylaxis.—The various forms of crutch dhobie's itch may be avoided by wearing next the skin short cotton bathing-drawers and changing them daily, at the same time powdering, after the daily bath, the axillæ and crutch with equal parts of boric acid, oxide of zinc, and starch.

Erythrasma is a chronic fungous infection of the stratum corneum caused by *Nocardia minutissima*, characterized by superficial lesions in axillæ and genitocrural regions, but occasionally involving other intertriginous areas. It occurs throughout the world, most commonly in the tropics. The lesions appear as punctate to palm-sized circumscribed maculopapular areas which vary from light brown to reddish-brown in colour, with a serpigenous erythematous border. In scrapings of the skin the fungus appears as short, delicate, branching filaments 1 μ or less in diameter. The morphological characters distinguish it from trichophyton and *Epidermophyton floccosum*. The treatment is the same.

Dhobie mark dermatitis is produced by fluid from the nut of *Semicarpus anacardium*, the ral or bella gutti tree and is known as *bhilawanol*, *chola gutti* in Assam, and *chela* in India. It is used by dhobies for marking clothes for laundering. It contains strong vesicants which withstand repeated washings

and causes local pruritus with dermatitis, erythema, vesiculation, and crust formation.

Cattle ringworms (*T. discoides*) when implanted in man produce *agminate folliculitis*, a sharply defined dull-red plaque with follicular pustules; *kerion*, an oedematous mass of discharging follicular pustules; *granulomata of majocchi*—irregular grouped nodules covered by red, unbroken skin.

RINGWORM OF THE FEET (HONGKONG FOOT; ATHLETE'S FOOT; MANGO TOE; BROCC'S ECZEMA; *TINEA PEDIS*); *TINEA OF THE HANDS*.

A peculiarly intractable infection of the feet, occurring especially amongst Europeans, is commonly observed in China and is known locally as "Hongkong foot," but now has a world-wide distribution; is found in



Fig. 151.—Ringworm of the foot with allergic eczema.

schools, athletic clubs, coal mines and the services, where communal bathing facilities are provided and is associated with conditions which produce hot, sweating feet. Gentles (1957) has clearly shown that the presence of dermatophytes on the floors of these bath-houses is most unlikely, but the spread of infection takes place by transfer of infected skin fragments which contain stable parasitic fungi, sometimes in large numbers. This mycotic infection, as identified by Dodd, is believed to be a variety of *Epidermophyton floccosum*, or, according to Beintemar, *Trichophyton interdigitale* or *T. rubrum*. It occurs especially during the summer months and appears as deep-seated vesicles about the inner margin of the hollow of the sole, or on, or between, the toes at their proximal extremities; or as a macerated condition of the skin of the interdigital clefts and of the contiguous surface. Scaling of the skin with persistent and intolerable

itching is a marked feature, and it often becomes secondarily infected (Fig. 151). Often a mycotic infection of the nails and the palms of the hands is associated with it, resembling Hebra's *eczema marginatum*, which is said to be due to *E. floccosum* and shows itself by closely set vesicles on the palms. Hyperkeratoses of the palms of the hands or soles of the feet, especially of the heel are also common. Isolation of the fungus presents difficulties owing to contaminating bacteria and moulds, but can be overcome by using potassium tellurite or penicillin to inhibit bacterial growth and by adjusting the reaction of the culture media to pH 10.5 to discourage the growth of moulds. A similar condition has been described in Turkish baths in England by Whitfield, and in swimming pools in the Southern United States, as well as among bathers in Holland. Tinea of the big toe or "Mango toe" is prevalent in the mango season in India and is also due to infection with *E. floccosum* and to transference from one person to another chiefly by bath mats. As a preventive measure the application of the following lotion is recommended:

Liq. formaldehyd. (40 per cent.)	3i	(3.5 ml.)
Acid. salicyl.	3i	(3.5 ml.)
Alcohol and water, equal parts .	3viii	(227.36 ml.)

Sulphomerthiolate powder (Lilly & Co.) should be dusted into socks after bathing.

Care must be taken to distinguish dermatophytids or allergic reactions which are superimposed upon foot ringworm, especially in *T. gypsum* infections. Where such reaction is present treatment must be directed on other lines; trichophytin skin sensitivity tests are useful in differentiation; treatment should be directed to the relief of inflammation and fungicides should be avoided till the acute stage has subsided. Potassium permanganate 1 : 4,000 should be used in cases with much vesiculation and applied before and after evacuation of the vesicles.

Treatment.—The application of Whitfield's ointment, after the feet have been soaked in hot water, is recommended : salicylic acid 1, benzoic acid 1, coco-nut oil 12, soft paraffin 16 parts. This ointment must be persisted with for three weeks or more. Castellani's 1 per cent. fuchsin paint is widely recommended.

Rademacher (1943) recommended the following treatment: 25 per cent. sulphathiazole in talc is dusted on to the lesions daily. Definite improvement appears within forty-eight hours. A commercial preparation consists of 5 per cent. sulphathiazole in a bland ointment and has been found satisfactory. All infected areas should be covered with a film of the powder. The criterion of cure is the healing of all lesions and disappearance of adherent cutaneous debris. In refractory cases 10 per cent. of powdered sulphathiazole is made up with 2 per cent. salicylic acid ointment. The course of treatment lasts from two weeks to one month.

Other authorities favour azochloramide in triacetin, 1 in 500. This penetrates some distance into the tissues and thus enables the germicide—azochloramide—to extirpate the deeper filaments. This preparation N-N—dichloroazo-dicarbonamidine, is a complex chlorine compound, which liberates chlorine slowly. Carbon tetrachloride may also be effective.

Mycil dusting powder (BDH) contains chlorphenecin, talc, zinc and boric oxides. *Sopronol* ointment is composed of sodium propionate, propionic acid, sodium caprylate, zinc caprylate and dioctyl sodium sulphosuccinate and is recommended. *Asterol* (Roche) and *Mersagel* (Glaxo) are fungicide jellies containing phenyl mercuric acetate (1 in 750). Another is *Merthiolate cream*, and also tincture of merthiolate, a solution of merthiolate in spirit, which sinks deep into the affected skin and thereby kills off the spores of the fungus.



Fig. 152.—Extensive *Tinea circinata* of legs (India).
(Philip Manson-Bahr.)

For eczematous complications the toes should be separated by strips of gauze, and the foot should be covered with it and kept constantly wet with glycerine of lead subacetate, 1 oz., glycerine, 1 oz. and water to 1 pint. This lotion can be later replaced by Lassar's paste. If a staphylococcal infection is present, dressings of acriflavine, 1 in 20,000, should be applied. Grisovin, the oral fungicide, is not so effective as in other skin fungus infections. The toe-web variety is especially so and treatment must be continued for months. (Brian Russell, 1960).

Infected patients should take careful precautions against the spread of the fungus, and should wear special slippers in the bathroom, and the feet should be dusted with 1 per cent. salicylic acid in talc. Loofah soles and bath towels are recommended as they can be sterilized by washing.

As a measure against re-infection the patient may wear cotton toe-caps, which must be boiled, and he should also have a rubber bath-mat for exclusive personal use.

Tinea circinata (Fig. 152), with its characteristic papilliferous rings, is the

most common ringworm of the tropics and may assume many different shapes and forms. They may be raised above the level of the normal skin or may be slightly elevated, particularly at the border. This is more usually inflamed and more scaly than the central portion. In some cases concentric circles develop or rings form upon one another making various patterns. The fungus whose spores and mycelial element can be seen in scrapings is known as *Trichophyton rubrum*, *T. mentagrophytes*, *T. sulphureum* or *T. violaceum*.

RINGWORM OF THE NAILS (*Tinea Unguium*)

This is a mycotic infection of the nails and is a comparatively common and extremely intractable condition in Europeans, especially in India and China; it may last for twenty years or more. It may occur as an independent affection, or secondary to ringworm of the skin, scalp or beard, and is often found in association with *tinea cruris*. One or all of the nails of both hands and feet may be attacked. The fungus is a trichophyton, usually *T. rubrum* or *T. mentagrophytes*. English (1957) has shown that the first signs of this serious infection are scaling or macerated areas between the toes indistinguishable from *tinea pedis*.

The fungus first attacks the epidermis of the nail-bed and gradually invades the nail matrix. In doing so it causes considerable discolouration, ridging and fissuring of the nail itself, which becomes opaque, with a brittle, frayed edge. The fungus may pass from the skin over the nail-fold and in this manner reach the matrix. It is apt to be a conjugal infection and children are specially liable to contract it.

Diagnosis.—The appearance of the affected nail is not sufficiently characteristic to be distinguished without microscopic examination. The disease is generally well advanced before it can be recognized. For microscopic diagnosis, scrapings of the nail are boiled in liquor potassæ, or left to soak for twenty-four hours. The scrapings themselves should be made as thin as possible with a piece of glass. The fungus can then be recognized in the softened nail débris, especially in small dark hæmorrhagic spots. For culture nail scrapings are first examined in 15 per cent. potassium hydroxide solution and cultured on Sabouraud's glucose agar with added penicillin and streptomycin. The diseases liable to confusion with ringworm of the nails are *eczema*, *syphilis* and, especially, *psoriasis*.

Treatment.—In the early stages, when the lunule is attacked, the disease may be stamped out by softening the affected portion with solution of potash, and painting with tincture of iodine or with a 2 per cent. solution of corrosive sublimate in alcohol, twice daily. When the nail is completely involved, cure is almost impossible save by extirpation or by avulsion. The result is, however, disappointing, as the new nail usually becomes infected in turn. After removal, the thickened nail-bed should be scraped, and the matrix dressed with a parasitocidal ointment:

Grisovin tablets in doses of 1.5 gm. daily are strongly recommended in this distressing condition. The antibiotic griseofulvin orally, endows newly formed keratin with the power to resist fungal attack. Brian Russell

and colleagues (1960) treated their cases for as long as three months to one year. Those with infected toe-nails are more refractory and only a small percentage of these can be cured by this method.

The shedding of the nails by application of X-rays is unsatisfactory. Less severe cases are treated by softening the nail-plate by wearing rubber finger-stalls containing soft soap for a few days; the softened nail is then scraped down as far as possible with glass, followed each time by the application of lint soaked in Sabouraud's iodine (iodine 5, potassium iodide 1, water 100), which should be kept in position by a loose rubber finger-stall.

TINEA TONSURANS (Ringworm of the Scalp)

This is very common in children, but rarely found in adults. It appears first as a small, greyish scaly patch, covered with broken hairs. The patches increase in size and number and may involve the whole scalp. It may be associated with tinea circinata.

The organism is *Microsporum audouinii*, but it was found by Ota (1922) that *M. ferrugineum*, first isolated in Japan, Manchuria and the Far East, is more characteristic of the true tropics and is found commonly in the Belgian Congo. It is an ectothrix.

On most mycological media the colony appears as a yellow to orange glabrous colony. On microscopic examination the cultures usually show only chlamydospores and swollen hyphæ. Takeya (1928) found it in 32 out of 51 cases in Tokyo, Kurotckin and Chung (1930) in 5.2 per cent. of 174 cases in Peking, while Mapleston and Dey (1939) have recorded 8 cases in Indian children in Calcutta; Leita (1947) found it as the cause of tinea capitis in Angola. It really occurs all over the world and has been identified in England. In treatment grisovin tablets, 1 grm. daily, have been found most effective.

MYCOSIS OF THE EAR (Otomycosis)

Mycosis of the external auditory meatus is popularly known as "Panama ear," "Surfer's ear," "Hot weather ear," or otitis externa diffusa, and more descriptively as "desquamative external otitis." It was of frequent occurrence in U.S. Army in World War II, especially in Guam. There is a racial predisposition especially in Caucasians and natives of temperate climes. The infection declares itself by soreness and redness of the external auditory meatus, with tenderness on contact and pain on chewing. Itching and pain may be intolerable. The external canal is coated with a moist, soft, sebaceous-like detritus. In the third stage the walls become swollen so that the canal is obliterated. The pain produced is worse at night and there is moderate pyrexia. Fungous mycelium and spores can be demonstrated in the detritus. Some authorities think that *Bact. pyocyaneus* is the chief factor. *Candida albicans*, *Malassezia furfur* and other fungi have been found.

In treatment the meatus is washed out with 4 per cent. boric acid solution through a straight a tic cannula attached to an all-rubber irrigating syringe. After washing, the ear is gently dried. When the canal is free from débris

the whole surface of the walls and of the tympanic membrane is painted with a mild astringent, such as 2 per cent. silver nitrate, or the canal is plugged with ribbon gauze and saturated with 10 per cent. boric acid ointment. This is the treatment for moderately severe cases, but for the most acute, local heat treatment, with injection of penicillin, is advocated.

TINEA IMBRICATA

Synonym.—Tokelau Ringworm.

Geographical distribution.—The affection is principally met in the Eastern Archipelago and in the islands of the South Pacific, where it affects a large proportion of the population. It has been found to extend westwards as far as Burma, and northwards as far as Formosa and Foochow on the coast of China. Cases have been reported from Central Africa and the interior of Brazil. Once introduced, it spreads very rapidly in countries with a damp, equable climate and a temperature of 80–90° F. Very high or very low temperatures and a dry atmosphere are inimical to its extension.

Ætiology.—On detaching a scale and placing it under the microscope, after moistening with liquor potassæ, a trichophyton-like fungus can be seen in enormous profusion. The parasite evidently lies between the stratum corneum of the epidermis and rete, and by its abundance causes the former to peel up. As the fungus does not die out in the skin travelled over, it burrows under the young epithelium almost as soon as the latter is reproduced. Hence the peculiar concentric scaling and the persistence of the disease throughout the area involved. When the scales are washed off by the vigorous use of soft soap and hot water, the surface of the skin is seen to be covered with brownish parallel lines—evidently the slightly pigmented fungus proliferating and advancing under the young epidermis.

The parasite, said to be of two varieties, *Trichophyton concentricum* (syn. *Endodermophyton concentricum*) and *T. indicum*, can be cultured by immersing the scales in alcohol for five to ten minutes and then placing them, one scale to each tube, in glucose broth. After five or ten days the scales, if uncontaminated, are transferred to solid media, and growth takes place in three or four weeks.

Symptoms.—Tinea imbricata may at first be confined to one or two spots on the surface of the body; usually, in a short time it comes to occupy a very large area. It does not generally affect the soles and palms, although it may do so; nor is the scalp a favourite site. Baker remarked that it avoids the crutch and the axillæ. With these exceptions it may, and commonly does, sweep over and keep its hold on almost the entire surface of the body, so that after a year or two a large part of the body is covered with the dry, tissue-paper-like scales, arranged in more or less confused systems of concentric parallel lines. This arrangement of the scales is absolutely characteristic of the disease (Plate XIX).

An inoculation experiment readily explains the production of the scales, their concentric parallel arrangement, and the mode of extension of the patches. About ten days after the successful inoculation of a healthy skin with tinea imbricata, the epidermis at the seat of inoculation is seen to be very slightly raised and to have a brownish tinge. Presently the centre of this brownish patch—perhaps a quarter of an inch in diameter—gives



TINEA IMBRICATA

(By permission of Medical Department of Sarawak Government.

way, and a ring of scaling epidermis, attached at the periphery, but free, ragged, and slightly elevated towards the centre of the spot, is formed. In a few days this ring of epidermis has extended so as to include a larger area.

The scales, if not broken by rubbing, may attain considerable length and breadth; but, of course, their dimensions are in some degree determined by the amount of friction to which they are subjected. Usually, they are largest between the shoulders—that is, where the patient has a difficulty in scratching himself. The lines of scales are from $\frac{1}{8}$ to $\frac{1}{2}$ in. apart.

Diagnosis.—From *ordinary ringworm*, *tinea imbricata* is easily distinguished by the absence of marked inflammation or congestion of the rings, by the abundance of the fungus, by the large size of the scales, by the concentric arrangement of the many rings or systems of rings, by the non-implication of the hair, and by the avoidance of crutch and axillæ. From *ichthyosis* it is distinguished by the concentric arrangement of the scaling, by the peripheral attachment of the scales, and by the presence of an abundance of fungus elements.

Treatment.—The best treatment for *tinea imbricata* in natives is the free application of linimentum iodi; its action is said to be increased by the addition of salicylic acid, 15 gr. to the ounce. Limited patches may be treated with chrysophanic acid ointment (20 gr. to the ounce), or by the more modern preparation, cignolin. Clothes should be boiled or burned.

Grisovin (Glaxo) tablets, 0.25 grm., containing the antibiotic, griseofulvin, when taken by the mouth, in doses of 1–2 grm. daily for 17 days have recently been proved to cure this fungus disease entirely.

Prophylaxis.—Daniels related that *tinea imbricata* is a comparatively rare disease in Tonga, and the natives attribute this to their custom of oiling the body with coco-nut oil. Since the Fijians adopted this practice the disease has become somewhat less prevalent among them. Personal cleanliness, and the immediate and active treatment of any scaling spot, should be carefully practised in the endemic countries. Amongst certain Central African tribes it has never been observed in women, who oil their bodies, whereas the men, who do not adopt this custom, are subject to the disease.

In Tahiti the use of chrysophanic acid is now general among the natives; as a consequence, the disease is less prevalent there than it was only a few years ago.

VII. SPIROCHÆTAL SKIN DISEASE AND AFFECTIONS OF THE HAIRS

PINTA

Synonyms.—Carate; Mal del Pinto.

Definition.—A spirochætal disease characterized by peculiar pigmented patches on the skin. "Pinta," a Spanish word to describe spotted or mottled appearance, was first used by Oviedo (1505–1516).

Geographical distribution.—Pinta occurs in certain districts in tropical America, especially along the river banks—in Mexico, Venezuela, Colombia,

Bolivia, and in one or two places in Peru, Chile, Guatemala, Honduras (Stamm Creek) and Brazil.

Ætiology.—For many years this peculiar skin disease was regarded as due to parasitic fungi. Menk (1926), on the high percentage of positive blood Wassermanns, suggested that it was a spirochætal disease. Saenz, Armenteros and Triana in Cuba (1938) found spirochætes in the skin abrasions, and Blanco (1938) obtained them by lymph gland puncture. To this spirochæte the name of *S. herrejoni* was given. This discovery was confirmed by Blanco (1938) in Mexico, by Iriarte in Venezuela (1939) and by León in Ecuador, who found the organisms especially abundant in the early papules. Brumpt (1939) proposed the name *Spirochæta (Treponema) carateum*. As there has been some confusion about the correct terminology, it is now considered that this name has priority.

This spirochæte, in measurement as well as in appearance (by dark-ground illumination), is closely allied to *S. pallida*. When first isolated it is very active, but its motility decreases in about twenty minutes. It is 12 to 18 μ in length, and easily stained by silver impregnation and by Giemsa stain. It is readily dissolved by saponin and dies in a short time in bile (Fig. 153).



Fig. 153. *Spirochæta carateum* (herrejoni). (After León y Blanco.)

Varela claimed that *S. carateum* has certain differences from most other spirochætes. When stained by Giemsa it has a flexible cylindrical form with pointed ends. The turns are 0.6–1 μ in width, 0.4–0.5 μ deep and 9–10 in number.

Animal inoculations.—The Venezuela Commission reported that inoculations in guinea-pigs, rabbits and rats were without result.

Varela and Olarte have shown that antibodies are present to *S. carateum* in the serum of pinta patients. There is no cross immunity between pinta and syphilis. Thus syphilitic chancres may be seen in pinta subjects, and pinta can be transmitted to syphilitics. Attempts to inoculate pinta subjects with yaws have been partially successful. Nevertheless antibodies to *S. carateum* are present in the serum of syphilitics.

Human Inoculations.—Blanco (1940) demonstrated, by inoculation into volunteers, that the disease is infectious and may be easily transmitted when a small amount of serum from a pinta lesion is injected. In syphilitic patients an initial papule developed, but the secondary eruption was atypical. Positive Wassermann reactions were obtained, but not before the appearance of the secondary eruption. The primary lesion differs from that of syphilis or yaws in that it is always closed and does not ulcerate. Experimental inoculations showed that previous syphilis does not give absolute immunity to pinta.

Pathology.—The spirochætes are chiefly located in the Malpighian cells, especially in small areas of acanthosis in the epidermis. A greater involvement of the corium has been described in pinta than in yaws, but much less than in syphilis. Spirochætes may be demonstrated in lymph obtained from glands near the lesions. The hair follicles and portions of the sweat glands are surrounded by inflammatory cells. The

pigmentary function is specially affected in pinta, and scanty pigment granules may be seen inside the cells of the stratum germinativum; they are also present in other cells of the Malpighian layer and in the melanophores of the dermis.

Symptoms.—There are three stages in the development of pinta of which the third is that of generalization. The first is an itching erythematous papule; the second discrete, circumscribed areas of pigmentation “particles”, and purple hyperchromic patches which are also seen in the oral mucosa; the third is distinguished by multiple, generalized areas of pigmentation (Fig. 154). The incubation period in experimental inoculations varies from 7–20 days, by which time an initial papule appears. This extends peripherally as a squamous, reddish patch, reaching a diameter of 1 cm. in a month, and then continues to spread peripherally. Secondary lesions appear in crops around the primary papule, spreading to other parts in about five months. Psoriasis-like, trichophytoid and lichenoid types are recognized. Progressive hyper-pigmentation is then observed; later still, depigmentation, which gives rise to various colours, or vitiliginous spots, ranging over the body. The colour of the lesions in order of frequency appears to be blue, white, mixed, lead-coloured, violet, black, red, or yellow. The spots vary in size and in shape: round, oval or irregular. They are not elevated, but are always strikingly visible (Fig. 155). The most marked subjective symptom is pruritus.

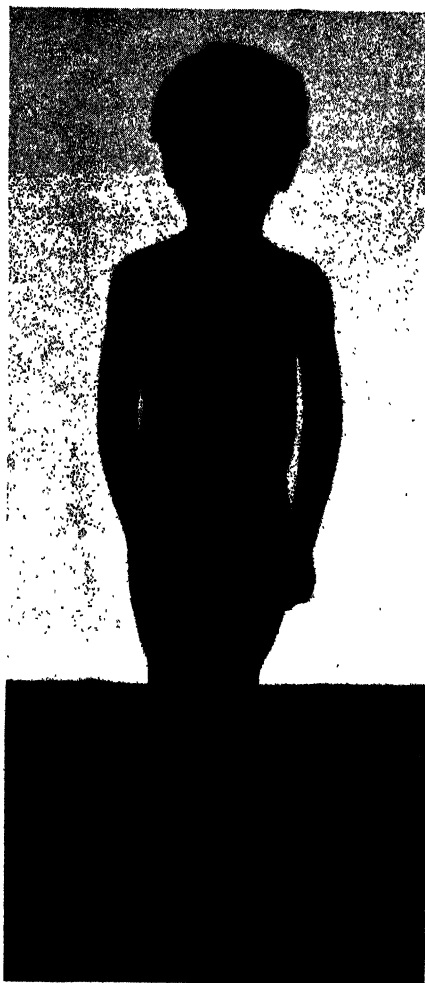


Fig. 154.—Pinta or Caratê in a boy.
(Dr. Armando Torvares, São Paulo.)

In natural infections the primary lesion is usually on an exposed part, particularly the legs and feet and arms, extending to the hands and face. According to Blanco, the initial lesion is never seen on the palms, or on the trunk. Modern observers divide the disease into three distinct stages, showing different clinical, serological and immunological features.

The primary stage occupies the period when the initial lesion is present and lasts from five months to one year. The secondary stage is characterized by skin lesions or papules which are rapidly converted into erythematous squamous lesions (named *pintids*) and ensues five months to one year from the time of infection. In the tertiary, or *dyschromic*, stage there are achromic or pigmentary spots, erythema, keratoderma and superficial atrophy. Super-infections may be produced by inoculations at this stage. Hyperkeratosis of palms and soles, as in yaws, are to be regarded as late manifestations (Fig. 156), but, according to Mazzotti, these are not found in Mexico, but may be due to a superinfection with yaws. Eosinophilia and an increase of basophil cells occur in a high percentage of cases. Onchogryposis, or pigmented changes in the nails is frequent.



Fig. 155.—Alveolar and punctiform type of Pinta depigmentation.
(Dr. L. A. León, Quilo.)

The exact relationship of pinta to syphilis is further complicated by the fact that Sænz in Cuba found aortitis, aneurysm and enlargement of the diameter of the heart and valvular lesions in 23.3 per cent. The association of this skin spirochaetosis with visceral syphilis is of course conceivable.

Diagnosis.—The characteristic spirochaetes are present in the lesions, but obviously it is impossible to differentiate them in their morphology from *S. pallida* or *S. pertenuis*. They are best demonstrated by expressing serum from the lesions by the application of narrow intestinal clamp forceps and examining with dark-ground illumination. Pinta is often associated with syphilis and yaws lesions, such as juxta-articular nodules. Sænz found changes in the cerebro-spinal fluid in 10 per cent. (increased globulin content and colloidal gold curve). There is no way of making a diagnosis serologically between syphilis and pinta.

Depigmented, or vitiliginous, areas are common in tertiary yaws and syphilitic lesions in the coloured races to which pinta is almost entirely limited. It is obvious that many other skin diseases have in the past been

confused with pinta. Apparently too many examinations have been made for the presence of fungi and micro-organisms without proper cleansing and disinfection of the skin.

Oteiza (1945) has described a reaction, by injecting the serum of early cases intradermally into the forearm of volunteers. An erythematous spot formed in from six to sixty-one days, about the size of a pin's head, often with satellite papules. Spirochætes were subsequently demonstrated in the lesions.

Differential diagnosis has to be made from leprosy, yaws, syphilis, erythrasma, pityriasis versicolor and other epiphytic skin diseases, and also from plain vitiligo or leucoderma.

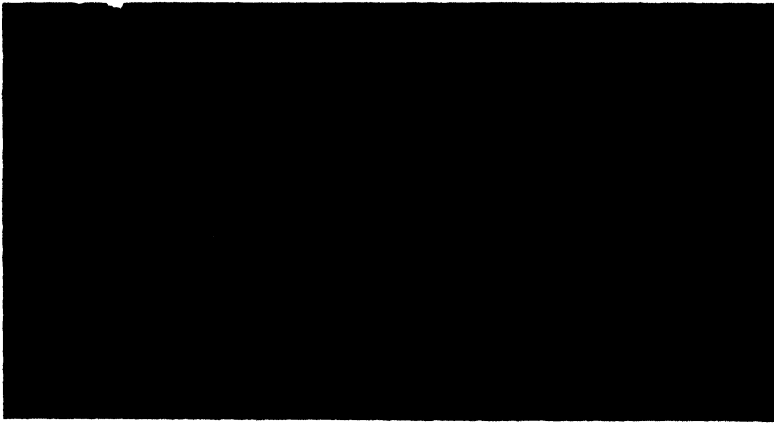


Fig. 156.—Hyperkeratosis of soles of feet in pinta. (Dr. L. A. León, Quito.)

Treatment.—The modern treatment for pinta is neosalvarsan, bismuth preparations and penicillin as described for yaws. The superficial skin lesions yield rapidly to penicillin up to a total of 3 mega units, but the atrophic vitiliginous spots remain unaffected, as in yaws. The Wassermann reaction in a proportion of cases remains positive after disappearance of the lesions. Oral administration of aureomycin causes the disappearance of *S. carateum* from the interstitial fluid obtained by pressure of the skin after excoriation of the epidermis (Mazzotti and Olarte, 1949).

TRICHOSPOROSIS

Synonym.—Piedra.

The black piedras are found in South America, chiefly in Brazil, Paraguay, Ecuador, Argentina, Uruguay, Colombia, etc. The small black nodule on the hair shaft is the ascostioma of the fungus *Piedraia hortai* belonging to the *Asterineæ*, a family of fungi parasitic on the leaves of trees in very humid climates. The nodules consist of tightly packed stroma of dark-brown hyphæ 4–8 μ in diameter; when crushed, asci containing fusiform curved ascospores are revealed. The white piedras are more widely distributed, being found in various countries of South America, Africa, Southern Asia, Japan and parts of Europe. The multiple

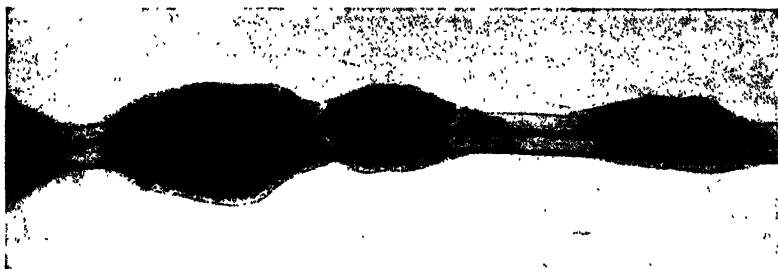


Fig. 157.—Human hair (magnified) affected with *Trichosporum beigelii*.

white nodules on the hair are formed of sclerotial masses of the mycelium of the fungus *Trichosporum beigelii* and other species, which are related to the common fungi known as *Geotrichum*, *Oidium* or *Mycoderma*. In contrast to black piedra this white form attacks chiefly the coarse hairs of the body (Figs. 157, 158).

Microscopically, the nodules, which are not so discrete as in black piedra, consist of a mass of polygonal cells, yellowish-green to brown, with a definite cell-wall. The cells of a mycelial thread are separated from one another by thick black cell-walls, between which there is little intercellular substance.

The hyphae tend to be perpendicular to the surface of the hair and segment into round or oval cells, 2–4 μ in diameter. Budding cells (blastospores) are also seen in the mycelial mass. Colonies of *T. beigeli* on Sabouraud's medium develop at room temperature and appear first as a cream-coloured, slimy growth which is soft in consistency.

Treatment.—The affected hair should be bathed twice daily with a lotion consisting of 1 dr. of formalin to 6 oz. of rectified spirit, reinforced by 2 per cent. sulphur ointment. The affected

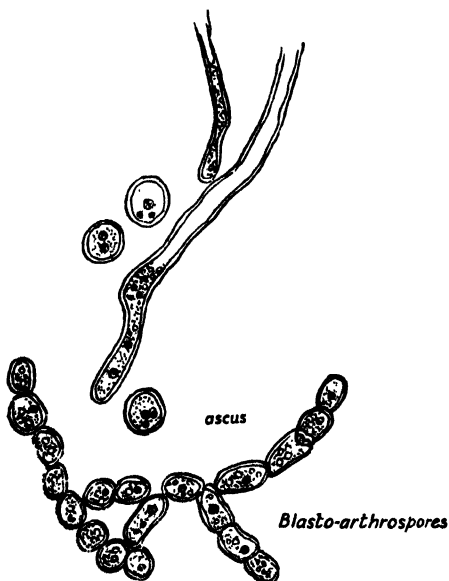


Fig. 158.—Fungus elements of *T. beigelii*.

surrounding skin should be rubbed with mercurial ointment.

TRICHOMYCOSIS

Synonyms.—Trichonocardiasis; Trichomycosis axillaris.

Trichomycosis is a fungous disease of the hair which in many ways resembles piedra. It may produce skin irritation and stain the clothes.

The shafts of the hairs, more especially those in the axilla, are attacked. Trichonocardiosis axillaris is common in many parts of the world, including England. It is caused by *Nocardia tenuis*, which produces a hard mucilaginous substance in which pigment-forming cocci vegetate, causing the distinctive black, red, and yellow varieties. *N. tenuis* is difficult or impossible to culture.

Treatment.—Consists of bathing with formalin and spirit and applying mercurial ointment.

VIII. SKIN DISEASES CAUSED BY ANIMALS

THE CHIGGER, OR SANDFLEA

This insect, formerly confined to the tropical parts of America (80° N. to 30° S.) and to the West Indies, appeared on the West Coast of Africa for the first time about the year 1872. Since that date it has spread all over the tropical parts of that continent, and even to some of the adjacent islands—Madagascar, for example. As a cause of suffering, invaliding, and indirectly of death from secondary infections, it is an insect of some importance. It is now extremely prevalent on the East Coast of Africa, and is causing a large amount of invaliding among the Indian labourers there by whom it has been introduced into India as far east as Kurachi, but in no other part.

The chigger (*Tunga penetrans*) is not unlike the common flea either in appearance or, with one exception, in habit. It is somewhat smaller (1 mm.), the head being proportionately larger and the abdomen deeper than in the flea. It is red or reddish brown. Like the flea, its favourite haunt is dry, sandy soil, the dust and ashes in badly kept native huts, the stables of cattle, poultry pens, and the like. It greedily attacks all warm-blooded animals, including birds and man. Until impregnated, the female, like the male, is free, feeding intermittently as opportunity offers. As soon as she becomes impregnated she burrows diagonally

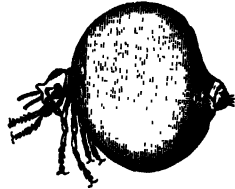


Fig. 159.—Chigger, [impregnated female. $\times 10$. (Blanchard.)



Fig. 160.—Section of female chigger in the stratum lucidum of the skin. (Fülleborn, Arch. für Schiffe-und Tropenhyg.)

into the skin of the first warm-blooded animal she encounters where, being well nourished by the blood, she proceeds to ovulation. By the end of this process her abdomen, in consequence of the growth of the eggs it contains, has attained the size of a small pea. (Figs. 159, 160.) As seen in Fig. 160, the chigger within the epidermis enters the stratum lucidum, which it invades and pushes before it. The epithelial layer becomes attenuated. The parasite becomes anchored in the corium by means of chitinous excrescences which stick out into the surrounding tissues. The first anterior and the two posterior segments do not participate in the enlargement, the latter acting as a plug to the little hole made by the flea on entering the skin. When the eggs are mature they are expelled by strands of muscular fibres which intersect the abdomen. They fall on the ground and, according to Hicks, the larva hatches on the third or fourth day; the first moult occurs on the fifth to eighth day

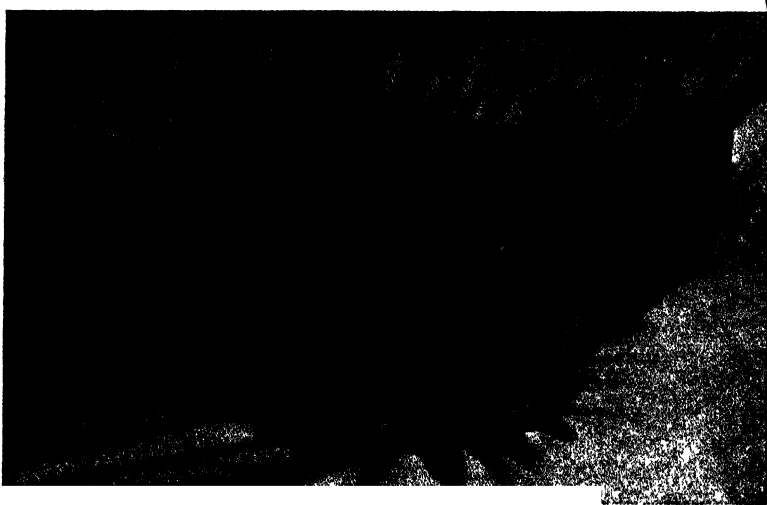


Fig. 161.—Septic lesions of foot caused by chiggers.

and preparation for pupation on the sixth to seventeenth days. The larva pupates at the same time, and the imago usually emerges about the seventeenth day. (See also Appendix p. 1087.)

During her gestation the chigger causes a considerable amount of irritation. In consequence of this, pus may form around her distended abdomen, which now raises the inflamed integument into a pea-like elevation. After the eggs are laid (according to some, before this process) the superjacent skin ulcerates, and the chigger is expelled, leaving a small sore which may be infected by some pathogenic micro-organism, such as the bacterium of phagedæna or of tetanus, with grave consequences. (Fig. 161.)

The chigger is not a good jumper and therefore she seldom attacks the skin above the dorsum of the foot.

The soles (Fig. 162), the skin between the toes, and that at the roots of the nails are favourite situations. Other parts of the body are by no means

exempt; the scrotum, the penis, the skin around the anus, the thighs, and even the hands and face, are often attacked. Usually only one or two chiggers are found at a time; occasionally they are present in hundreds, the little pits left after their extraction, or expulsion, being sometimes so closely set that parts of the surface may look like a honeycomb.

Ulceration is common, and may follow removal of the chigger or natural extrusion of the egg-sac. The ulcer commences as a tiny pit and, as it extends, the sloping edge may develop into a septic ulcer. It remains more or less circular in outline, except under the nail or nail margin, where the

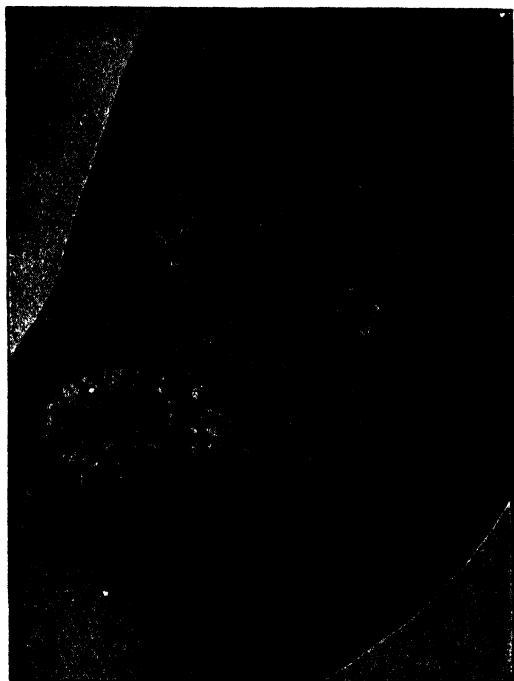


Fig. 162.—Chiggers in sole of foot. (Dr. C. W. Daniels.)

outline is more irregular and a pocket of pus forms underneath it. Chronic absorption of pus may lead to thrombophlebitis.

Treatment.—In chigger regions the houses, particularly the ground floors, must be frequently swept and accumulations of dust and debris prevented. The housing of cattle, pigs, and poultry demands the same precautions. The floors should often be sprinkled with carbolic water, pyrethrum powder, DDT, or similar insecticide, and walking bare-footed must be avoided. A daily bath must be taken, and any chiggers that may have fastened themselves on the skin at once removed. They may be killed by pricking them with a needle, or by the application of chloroform, turpentine, mercurial ointment, or similar means, after which they are

expelled by ulceration. The best treatment, however, is not to wait for ulceration, but to enlarge the orifice of entrance with a sharp, clean needle and neatly to enucleate the insect entire. Some native women, from long practice, are experts at this little operation. The part must be dressed antiseptically and protected until healed. Europeans living in an endemic district should wear high boots. A daily inspection of the feet, especially under the nails, is advisable. Should any black dot be discovered, the chigger should at once be removed.

Prophylaxis.—If avoidable, camps should not be formed in chigger-infested spots or in the neighbourhood of native villages. The camping-ground should be swept or, if necessary, fired; the floors of huts and tents may be sprayed with DDT and naphthaline, and native tobacco dusted

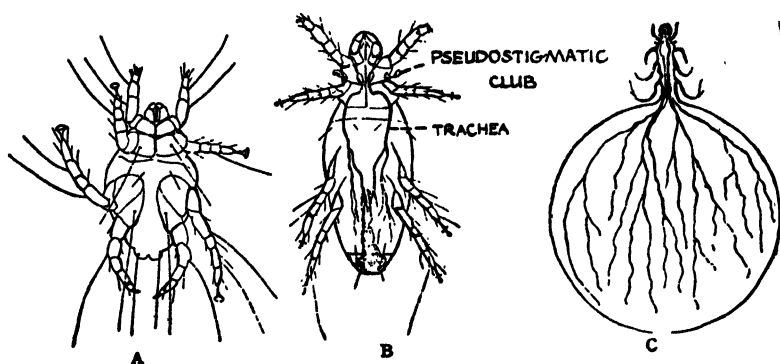


Fig. 163.—*Pediculoides ventricosus*. $\times 80$. (After Alcock.)

A, Male; B, adult female; C, pregnant female with brood-sac.

inside boots or shoes. Balfour recommended that the feet be rubbed thoroughly with a mixture consisting of 5 drops of lysol, or liq. cresoli sap., in 1 oz. of vaseline. Special attention should be paid to the interdigital clefts. Pigs should not be kept in the vicinity of dwelling-houses, as these animals are severely attacked by chiggers.

ACARINE DERMATOSIS

Several forms of mites inhabiting sugar, grain, or copra may live as temporary parasites on the skin of man, and set up an intense irritation not unlike that produced by scabies. One of the most familiar of these is "grocer's itch," set up by mites of the genus *Glycophagus*, which are common in raw sugar and cause an erythematous rash. Among the copra workers in Ceylon and the Pacific islands a similar skin affection is due to *Tyroglyphus*. "Grain itch," an urticarial and papular eruption of the exposed parts of the body, is caused by *Pediculoides ventricosus* (Fig. 163, A, B, C) in those who handle grain, cotton-seeds, or beans. These mites give rise to a severe pruritus. Preventive treatment consists in the application of 5 per cent. beta-naphthol ointment, and dilute carbolic acid to kill the mites.

NUNEZ ANDRADE'S DISEASE

A parasitic dermatitis resulting from the bites of the larvæ of *Neoschönastia nunezi* is found in Brazil. Molluscoid lesions are accompanied by internal pruritis. This insect, 0.33–0.45 mm. in length, is a common parasite of fowls and produces petechiæ of the skin resembling spots of ground brick.

Hæmatosiphoniasis in Mexico is due to bites of *Hæmatosiphon inodora*—locally known as *Chinche de los gallos* (Chicken bug), an insect 5×3 mm., which is greenish-red in colour. It produces a polymorphous dermatitis with pustules, scabs and linear scars.

BUTTERFLY, MOTH DERMATOSES, BEETLE AND CATERPILLAR DERMATITIS

Leger, Mougels and Bozé have described urticaria, conjunctivitis and facial oedema due to contact with a saturniid moth, *Hylesia urticans*, in French Guiana. In Celebes similar lesions are evoked by another, *Scirpophaga innotata*. The dorsal side of the wings of this moth are covered with a greyish-white powder which is the irritating agent.

Le Gac and colleagues describe a similar dermatitis due to a moth, *Anaphe renata*. The imago and the larvæ are clothed with detachable irritating hairs. Africans as well as Europeans are affected in French Equatorial Africa. Similar moths occur also on the Gold Coast. In Brazil flannel moths (*Megalopygidæ*) are well known.

In Texas the "Puss caterpillar" *Melagopyge opercularis* produces thousands of cases of dermatitis in children necessitating the closing of schools.

In Japan it was reported in 1955 that the poisonous moth *Euproctis slava* had affected 800,000 people, two-thirds of them in Nagoya.

In Israel every year caterpillar dermatitis is prevalent in the months of February and May caused by the hairs of *Thaumata poea pinivora*.

The nests of moth appear in pine trees and have become more numerous as the result of afforestation. Skin-irritation and conjunctivitis last 2–8 days. Only the hairs of the caterpillar contain the irritant. Bercovitz (1946) described epidemics of urticaria in troops in New Guinea and others have been recorded in N. Australia due to a moth, *Ochrogaster contraria*. Some developed urticaria within a few minutes. Caterpillar urticaria is common in the Panama Canal Zone due to *Megalopygida lanata* which produces rapidly-developing eosinophilia (8–22 per cent.), numbness and vesication. It is pale yellow, 5 cm. long by 1½ cm. The body is covered with long black hairs.

Beetle dermatitis.—Canthariasis, or infection by blister beetles, can take place at any stage of the cycle and may produce intestinal, urinary, ocular and cutaneous varieties. These are beetles of the family *Meloidæ* which contain a cyclo-toxic principle—*cantharides*, which, when applied to the skin, produces vesicular dermatitis. The Staphylinidæ (rove beetles) embrace forms with vesiculating properties. They occur in Java, Tropical S. and E. Africa and in S. America.

Two species of Sessinea (coconut beetles) cause burning pains at point of contact, followed by large blisters.

Earle has described "Fuetazo dermatitis" in those engaged in oil exploration on the Coast of Ecuador. This is caused by a blackish-green beetle (*Pœderus ornaticornis*), 1 cm. in length. "Fuetazo" is Spanish for whiplash.

A variety of lesions are caused by contact with the secretions of this insect, the most common of which is a papulo-vesicular rash.

BEE AND WASP STINGS

The stings of hymenoptera of the tropics resemble those of temperate climates, but can be more severe. Stinging bees, *Apis indica* and *A. florea*, the small bee, as well as the giant Indian bee, *Apis dorsata*, may attack in swarms in temples and caves, stinging many people to death. In N. Africa the species is *A. mellifica addisoni*. The antidote is injection of adrenalin. Sensitization may ensue leading to anaphylaxis which may be fatal. A parasitic wasp in Tokyo is *Scleroderma nipponensis* of which the female is ant-like and wingless. In one incident 340 people were attacked causing reddish swellings and injuries leading to suppuration and lymphangitis.

Massive anaphylaxis causes muscular paralysis and suggests a curare-like action at synapses of muscle-end plates. Hymenoptera venoms contain histamine, acetyl-choline and enzymes. 5-hydroxy-tryptamine is a constituent of wasp venom which is distinctly more active than that of the honey bee.

Marshall (1957) finds that toxic reactions resemble those of rattlesnake poisoning with hæmolytic and neurotoxic effects. Allergic shock develops quickly, in the course of 20-30 minutes. In bees hypersensitivity is believed to be due to water-soluble protein derived from its body. Wasps, being scavengers, may introduce bacteria with their stings.

Section VIII.—LOCAL DISEASES

CHAPTER XLIII

TROPICAL PYOMYOSITIS—RHINOSPORIDIOSIS—RHINO-SCLEROMA—AINHUM—BIG HEEL—ONYALAI—CHIUFA—TROPICAL EOSINOPHILIA

I. TROPICAL PYOMYOSITIS

Synonyms.—Myositis Purulenta Tropica; Tropical Myositis; "Bung-pagga" (Patton).

Ætiology.—The infection was regarded by Pawan as secondary streptococcal and staphylococcal infection in filaria-infected subjects. Von Bormann thought that the organism was a hæmolytic staphylococcus, usually *S. aureus*, less commonly *S. albus*. Erasmus in East Africa found the former most frequently. In the Editor's experience these two organisms are responsible, though occasionally *Streptococcus pyogenes* is found as well.

The site of entry is uncertain, but dissemination appears to take place by the bloodstream, for the lymphatics and lymph glands may show no sign of inflammation.

Associated infections.—Pyomyositis is more apt to occur in persons who are debilitated as the result of some other longstanding infection. In the Editor's experience this has been either ancylostomiasis, malaria, and, in a proportion, syphilis. In his series of cases the Wassermann reaction was positive in 50 per cent. One of the chief aims of treatment should be the eradication of these concomitant infections, and, wherever necessary, antisiphilic treatment with salvarsan and penicillin should be instituted.

Symptoms.—Several types may be distinguished.

Acute non-suppurative stage.—An indurated, tender, ill-defined mass can be felt in the affected muscles where the patient complains of pain. There is usually slight pyrexia, with inflammatory reaction over the neighbouring tissues and pitting œdema. On incision the tissues are œdematous, whilst the regional lymph glands are usually enlarged and tender.

Acute suppurative stage.—The clinical features are those of a deep-seated abscess, and, on incision, large collections of pus in the affected muscles are evacuated. The abscess cavity is loculated, requiring a wide incision and the breaking down of septa formed of dense indurated muscle, or fibrous tissue. The numerous sloughs in the cavity are characteristic. These abscesses occur in widely separated sites: in the thigh muscles, pectoralis major, serratus magnus, latissimus dorsi, gastrocnemius, flexor muscles of arm, iliopsoas and internal oblique. Generalised septicæmia may result.

Chronic abscesses have been recorded in the adductor magnus.

Diagnosis.—The diagnosis of pyomyositis should not present any great difficulty, but it has to be differentiated from gummatous suppuration, filarial abscesses, glanders, melioidosis, rheumatic nodules and swelling, osteitis of femur, cold abscesses of sacro-iliac joint, septic mastitis, perinephric abscess and fibrosarcoma.

Treatment.—Under modern conditions treatment consists of essential surgical incisions and the administration of antibiotics. Vigors Earle (1946) has proved the efficacy of penicillin by injection of 2,000 units two-hourly up to 11 doses. Penicillin treatment is indicated wherever pyomyositis occurs.

II. RHINOSPORIDIOSIS

Definition.—A disease due to a yeast-like organism, *Rhinosporidium seeberi*, which infects the mucous membrane of the nose, producing nasal polypi and tumours on the cheek, conjunctiva, lacrymal sac, uvula, ear, glans penis and skin. Some authorities now regard it as a protozoon.

This parasite has now been recorded from India, Ceylon, Argentina, Paraguay, and Uruguay, Uganda (Mowat and Hennesey, 1941), the United States, Ecuador, Malaya and Indonesia.

Ætiology.—*Rhinosporidium seeberi* (Wernicke, 1903) is a spherical or oval non-motile organism which occurs in polypoid growths, usually lying between the connective-tissue cells. The earliest stages are about $6\ \mu$ in diameter, with a chitinous envelope, vacuolated cytoplasm, and vesicular nucleus containing a karyosome (Fig. 164, A, B). When fully-grown, the cyst, or sporangium, may measure 0.25–3 mm. in diameter, but when half-grown the nucleus commences to divide by binary fission, until thousands are produced, of which the majority become daughter-spores, though a considerable proportion remain unchanged. The fully-formed sporangium (Fig. 164, C) finally bursts and discharges the spores, which are enclosed in chitinous envelopes; they then spread into the connective tissues via the lymph channels, and on reaching suitable spots the trophic stage at once begins and the cycle is repeated.

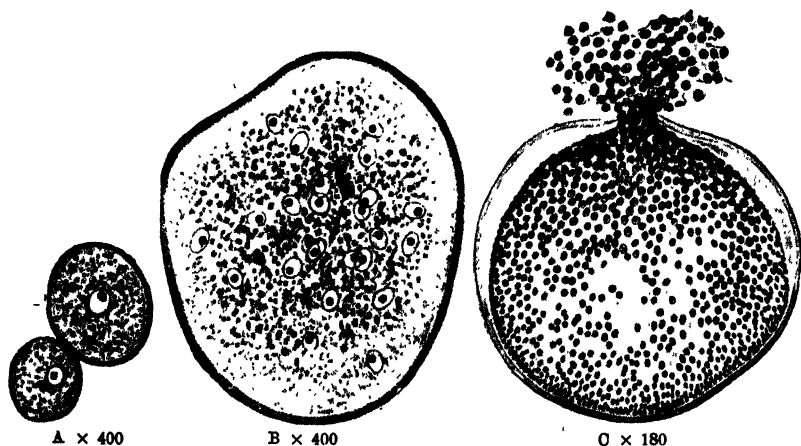


Fig. 164.—*Rhinosporidium seeberi*. (After Ashworth; by permission of Roy. Soc. of Edin.)

A, Trophic stages. B, Section of a stage with 64 nuclei, 24 of which lie in this section. C, Sporangium from which spores are being discharged, accompanied by mucoid substance, through a wide orifice. The first spores to issue (those near the opening) are followed by the central spores. The peripheral spores lie in a fairly firm mucoid matrix. Stretching of the envelope, due to growth of the sporangium, has not only reduced its thickness, but has almost caused the disappearance of the thickened annulus round the pore.

Attempts at cultivation proved partially successful in Ashworth's hands, and multiplication of the spores took place, but slowly, on Sabouraud's medium.

The mode of transmission of this parasite is undetermined, but the occurrence of a closely related organism, *R. equi*, in the nasal cavities of the horse is suggestive. Ayzar in India has found it in the noses of cattle (1925).

Allen (1936) has figured multiple pedunculated tumours on the nose and face generally and has described one case in particular with secondary tumours on both feet which ultimately became distributed over the whole body.

Rajam (1955) found hæmatogenous dissemination and demonstrated cells in the urinary sediment, peripheral blood and ascitic fluid.

Agrawal and Shama (1959) have described nodules on palate, lower eyelids and visceral involvement in lungs, liver, spleen and skin.



Fig. 165.—Rhinoscleroma of two years' duration in an Egyptian woman.
(Dr. H. K. Giffen.)

Treatment consists in removing the polypi from the nares by a wire snare. Medical treatment does not appear to be indicated, although Wright reported that the tumours disappear after intravenous injections of tartar emetic. Allen (1936) used neostibosan though it is not always effective. A popular native remedy is a snuff composed of tobacco leaves and lime.

III. RHINOSCLEROMA

Rhinoscleroma (*Scleroma respiratorium*) (Fig. 165) is a well-marked disease in all its aspects, pathological or bacteriological. It is a disease of unhygienic surroundings and has a world-wide distribution, but at the present day is much commoner in the tropics than elsewhere. It takes the form of spontaneous, painless, and exceedingly chronic inflammatory growths occurring at any place in the respiratory passages from the nostrils to the hilum of the lung. Gross deformity of the nose, or narrowing or distortion of the respiratory passages results. The typical splayed-out

organ is known as the "Hebra nose" and is most commonly found in Sumatra, but is rare elsewhere. Sometimes there is perforation of the nasal septum with total destruction of the uvula. The process extends along the respiratory passages with little change in the surrounding tissues. On the whole, it tends to form metastases with enlargement of the neighbouring lymphatic glands, but, in spite of this, the general health and condition remain unaffected.

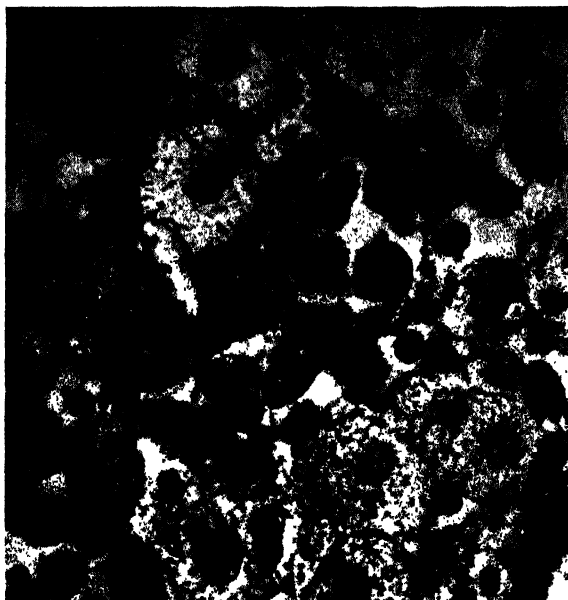


Fig. 166.—Rhinoscleroma: Photomicrograph of tissue, showing Mikulicz cells and general histological picture. (Dr. H. K. Giffen.)

Geographical distribution.—Rhinoscleroma is spread over widely distributed regions in special nests, or foci, but occurs all over the world. According to Kouwenaar (1956) there are between 3,000–4,000 cases of this disease. Small foci exist in Switzerland and Italy. The most extensive region is in Eastern Europe, in Hungary, Poland, Galicia, the Ukraine and the northern shores of the Black Sea and Caspian. Other foci have been noted at Tomsk in Siberia, in Turkestan, Bengal, Java, Sumatra, central and southern France, Morocco, Egypt, North America (in New England states), Argentine, Cuba, Mexico, Panama, Colombia, Brazil, Peru, Chile, El Salvador and Costa Rica.

Ætiology.—The cause of rhinoscleroma is undoubtedly *Bacterium rhinoscleromatis* described by V. Frisch in 1882. It is closely related to *Streptococcus pneumoniae* of Friedlander from which it can be distinguished by its growth as well as by its reactions in media containing bile. It is usually Gram-negative. It is easily cultivated, and forms knob-like

colonies on gelatin or agar, greyish on the whole, and less conspicuous than *S. pneumoniae*. It usually coagulates milk, and forms acid freely with lactose. In sections, it is found in hard fibrotic swellings in the nose, scattered throughout the mucosa and submucosa. It has so far been found impossible to reproduce the lesions by inoculation, either in man or animals. In fact, it exhibits a very low order of pathogenicity for laboratory animals, with the exception of mice.

It has to be differentiated from other encapsulated pneumococcus-like organisms in the nose.

Pathology.—Rhinoscleroma is characterized by a peculiar form of plasma-cell infiltration of great density, and by gaps or "fat-cells," which are found to consist of swollen cells with foamy cytoplasm ("foam-cells" or "Mikulicz cells") (Fig. 166). Very frequently, also, there are hyaline-drops or Gram-positive "Russell's bodies," which occur in all kinds of degenerative tissues, and are probably derived from the plasma cells. The rhinoscleroma nodule is known as plasmoma (Unna); it never breaks down, but becomes progressively sclerosed.

The scleromatous process may spread and, via paranasal sinuses, may grow into the upper lip and infiltrate the alveolar process of the maxilla, involve the pharynx by direct extension from the nose and may affect the lacrymal duct. The cervical glands are often enlarged.

Diagnosis.—The appearance of the patient is sufficiently suggestive and the Dutch in Java found the complement-fixation test most reliable. A rapid method of diagnosis is that of Barylak (1949) who teases out a portion of tissue, forming a smear and then stains it by Pappenheim's method. Characteristic foam cells can thus be demonstrated within 30 minutes.

Treatment.—The treatment is mainly by plastic operation to remove the unsightly outgrowths.

Various other methods, the most important of which is X-ray therapy, have been tried. Until the discovery of streptomycin the treatment of this condition was discouraging. Kouwenaar and others now believe that this antibiotic is specific either by the mouth or by parenteral injection in the generally accepted dosage.

IV. AINHUM (SPONTANEOUS DACTYLOSIS)

This is a very peculiar disease affecting the toes, particularly the little toes, of negroes, East Indians and other dark-skinned races, both in the Old and the New World. The name, derived from the Naga dialect, means "to saw or cut." An important contribution is that by Keen and colleagues (1946) in a clinical summary from Panama of 45 cases during a forty-year period. The disease occurred in adult active and otherwise healthy West Indian negro males, the incidence being 1.5 per 10,000. Tidy has described ainhum of the toes in three members of a Lebanese family from Beirut. Findlay has described pseudo-ainhum as due to nerve damage.

Symptoms.—The disease commences as a narrow groove in the skin, almost invariably on the inner and plantar side of the root of the little toe or little finger. Sometimes it may be bilateral. The association with hyperkeratosis palmaris was first noted by Spencer in 1942. It may occur in one foot only, or in both feet simultaneously, or it may affect one foot after the other. The groove, once

started, deepens and extends gradually round the whole circumference of the toe. As it deepens—perhaps, though not necessarily, with ulceration—the distal portion of the toe is apt to swell to a considerable size, as if constricted by a ligature (Figs. 167, 168). There may be no pain, but Kean asserts that it may be pronounced and progressive. There is inconvenience from the liability to injury to which the dangling and now everted toe or finger is exposed. In the course of years the groove slowly deepens, and finally the toe drops off, or is amputated. The groove may or may not correspond with a joint. In rare instances, after the two distal phalanges have dropped off, or been amputated, the disease recurs in the stump, and the proximal phalanx in its turn is thrown off. Of the other toes, the fourth is the one which is most frequently affect



Fig. 167.—Alnium.



Fig. 168.—Alnium at its height.
(Dr. A. B. Filho.)

very rarely is the third, second or great toe attacked. In the Army Medical Museum at Washington, U.S.A., there is a wax model representing a case of this or a similar affection, in which all the toes had been thrown off and the disease was making progress in the leg.

Occasionally, the terminal phalanx of the fifth digit of the hand has been affected. No relationship to leprosy, yaws, scleroderma or syphilis has been noted.

Alnium of the fingers should be known as *keratoderma hereditarium mutilans* (Vohwinkel).

Alnium is very rare in women or children, being most common in adult males. It runs its course in from one to ten or even more years.

On section, it is found as a rule, though not invariably, that the panniculus adiposus of the affected toe is much hypertrophied, that the bone is infiltrated with fatty matter, and that the other tissues are correspondingly degenerated. Sometimes the bone is thinned, or even altogether absorbed. At the seat of constriction a line of hypertrophy of the epithelial layers, and of atrophy of the papillary layer of the skin, together with a band of fibrous tissue, more or less intimately connected with the derma, surrounds, in whole or in part, the narrow pedicle.

Treatment.—It has been suggested that division of the constricting fibrous band would delay the evolution of the disease. In the early stage this might

be tried. When troublesome, the affected toe should be amputated. It is said that the application of salicylic ointment delays the process in the earlier stages (Moreira).

V. ONYALAI (ESSENTIAL THROMBOCYTOPENIA)

Under this title Massey and, later, Wellman (1904) originally described a peculiar disease occurring among the natives of Portuguese West Africa. Since then it has been recognized in East Africa, Tanganyika, on the Congo, and in Northern Rhodesia, where it is known as "Chipola," "Kafindo," or "Akembe," (bleeding disease—Wallace). It is especially frequent in Africa, though Preston Maxwell, in 1901, described a somewhat similar condition in the Fokien region of South China. It is now acknowledged to be identical with essential thrombocytopenia. It is characterized by formation of a number of vesicles, distended with blood, from $\frac{1}{2}$ to $\frac{3}{4}$ in. in diameter, on the hard palate and on the inside of the cheeks. Some of them are uniliculated. They differ from ordinary blood blisters by the presence of numerous trabeculae and by the semicoagulation of the contents which makes the vesicle difficult to empty. Occasionally it is accompanied by fever and most cases, with some exceptions, recover within a week or ten days. In a recent study in S. Africa, Metz and colleagues found the mortality of their series (57) was 5.3 per cent. The disease in S. Africa has a seasonal incidence from October to May.

The majority of victims are young adults. The onset is sudden and the early symptoms are lassitude, general dullness, and suffusion of the conjunctivæ, with pyrexia, sometimes of 103–104° F. There is tenderness over the parotids and vague pains. These are soon succeeded by widespread hæmorrhages into the skin and mucous membranes. In natives the cutaneous hæmorrhages are most easily seen in the axilla. Stein and Miller remark the constant association of cutaneous *purpura*, which is easily missed on black skins. Bullæ are seen on the lips, buccal mucosa, tongue, and palate, the last-named in particular. Epistaxis occurs in practically every case and subconjunctival hæmorrhages are in evidence. Bleeding occurs from the bowels as well as from the bladder, and blood may be observed in the urine or in the stools. In woman the periods are profuse. The patient becomes exsanguinated. At autopsy hæmorrhagic vesicles are found in the serous membranes, the pleura, peritoneum and diaphragm. A common finding is hæmorrhagic bronchopneumonia. Usually there are large retroperitoneal perirenal hæmorrhages. Blackie found involvement of the central nervous system in one of his cases. The bleeding time is increased, and there is a reduction in blood platelets to 20–30,000 per c.mm. Bleeding time is usually longer than 15 minutes (average 2–4). Sternal puncture shows increase of megakaryocytes with hyalization and failure of budding. Erythrocytes may be reduced to 800,000 per c.mm., leucocytes to 3,600. Normoblasts are usually numerous. The blood sedimentation rate is slightly increased. In Africa it extends from the equator to 26° south latitude, Johannesburg being the most southerly point. Stein and Miller (1943) studied 21 cases which could be classified as mild, severe or acute. The youngest patient was a native female aged 7 months. There is clear separation of acute and chronic types, the course and prognosis of which differ; the proportion being 7.4 : 1. Response to treatment is similar to the acute incipient episodes of idiopathic thrombocytopenic purpura.

Onyalai is not a deficiency disease and it is not, as has been asserted, due to poisonous native medicines.

The diagnosis has to be made from snake-bite, in which hæmorrhagic symptoms may supervene.

Blackie found that the most effective treatment was by blood transfusions and by injection of 18 ml. of donor's blood intramuscularly into the buttocks

or outer aspects of the thighs, but Stein and Miller found the intravenous route better. They suggest that splenectomy is indicated in patients who relapse after this treatment.

A.C.T.H. or corticotrophin, has given favourable results in treatment, and with its aid the bleeding time has been restored to normal.

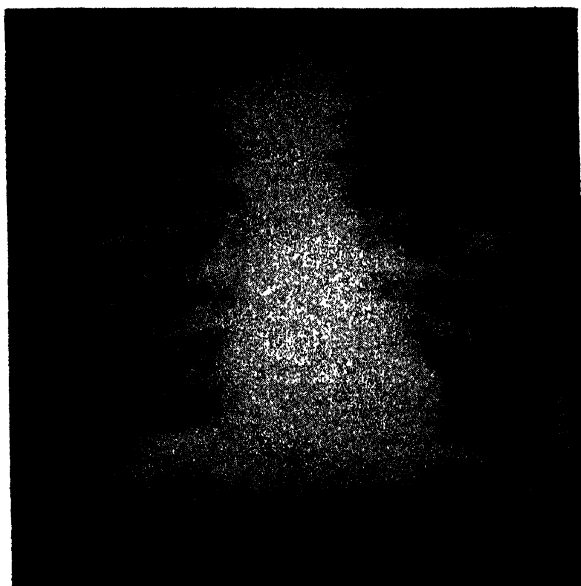
VII. TROPICAL EOSINOPHILIA (PULMONARY EOSINOPHILOSIS)

Under the name of pseudotuberculosis of the lung, with massive eosinophilia, a new entity was described by Frimodt-Møller (1940) and Weingarten (1943) in India, but has now been found in Ceylon, Malaya, North West and Central Africa, Tanganyika, China, the Philippines, Samoa, S. United States and other places. The subject has best been summarized by T. J. Danaraj in a thesis in Singapore (1951). This is characterized mainly by spasmodic bronchitis, leucocytosis and high eosinophilia. The physical signs are those of bronchial asthma. Males are more often affected than females. The common age is from twenty to thirty. Preliminary symptoms are cough, lassitude, dyspnoea on exertion, heaviness or pain in the chest palpitations; occasionally hæmoptoe (Viswanathan). There is usually considerable loss of weight (Menon). During the febrile periods the spleen is moderately enlarged. The most striking feature is massive eosinophilia, which accounts for the considerable leucocytosis up to 60,000 per c.mm. It may reach 90 per cent. and is higher than in any other disease, except eosinophilic leukaemia. The E.S.R. is raised in 75 per cent. A positive Paul Bunnell reaction often occurs. According to Viswanathan an acute and a chronic type can be recognized. The X-ray shows disseminated mottlings in the lung, the average single focus being the size of a split pea, somewhat similar to silicosis. The pathology is essentially eosinophilic bronchitis and bronchiolitis. There are dark reddish-brown areas scattered over the surface of the lungs. The most striking lesions are tubercle-like nodules with groups of giant cells in the centre and clusters of surrounding monocytes. Differentiation of tropical eosinophilia, according to Weingarten, from asthmoid bronchitis and Löffler's syndrome, is as follows: First there is no leucocytosis, and only moderate eosinophilia without pulmonary infiltration, whilst in the second the clinical and radiological signs disappear rapidly and spontaneously. It has a seasonal incidence, occurring in temperate climates as well as in the tropics. Cold agglutinins are present in the serum in high titre (Viswanathan, 1949). Tropical eosinophilia is usually benign and lasts for years, but reacts, to some extent to intravenous injections of neoarsphenamine in courses of six doses of 0.15 to 0.45 gm. It may well be that the term includes cases without pulmonary involvement. (Webb, 1960.)

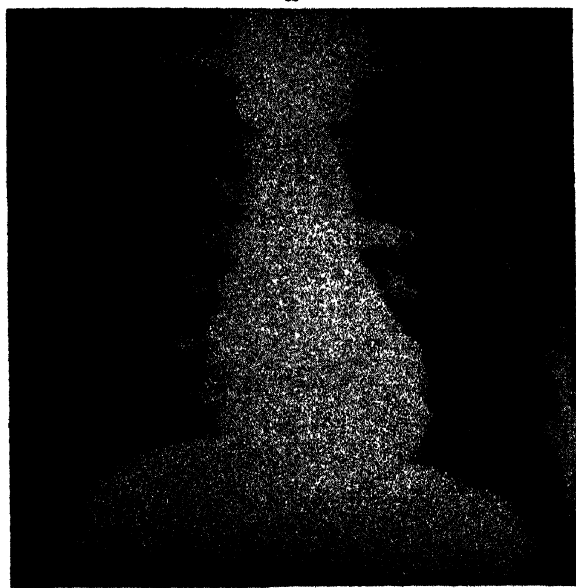
Danaraj (1956) has shown, in a striking manner, instantaneous response to hetrazan (banocide). In 10 selected ones there was a persistent eosinophilic leucocytosis with an elevated sedimentation rate. All were in Indian males.

The dose of hetrazan was 12 mgm. per kgm. for four days, in divided doses, three times daily with 50 mgm. tablets. The average dose was 200 mgm. three times daily. Improvement was noted in all about the end of the third day after commencement of treatment. There was complete relief of pulmonary symptoms and the fall in the eosinophilia began on the second or third days and continued steadily through ten days. The radiological picture became normal (Fig. 169 A & B). Moreover the filarial complement-fixation reaction, which had been strongly positive, became negative.

The possibility of a human filarial aetiology had already been advanced on the basis of the histological findings of microfilariae (*Brugia malayi*) in the lymph nodes of patients with hypereosinophilia, lymphadenopathy and pulmonary symptoms (Meyers and Kouwenaeer, 1939; van der Sar and Hartz, 1945).



A



B

Fig. 169.—Tropical Eosinophilia. Radiograms of lungs.

- A. Before treatment, showing typical striations and mottling. Indian male. W.B.C. 34,400. Eos. 66% (22,704). E.S.R. 44.
B. Same male as in A after treatment with hetrezan. W.B.C. 7,200. Eos. 23% (1,646). E.S.R. 10. Asymptomatic one week after commencement of treatment.

(*Dr. T. J. Danaraj*)

It has now been amply confirmed by Webb, Job and Gaunt in Vellore (India) in 1957 and 1960, when microfilariae, probably those of *B. malayi*, have been demonstrated by lung and liver biopsy, together with the typical cell picture, eosinophilic exudate, eosinophils and multinucleated giant cells.

In 1958 the appearances of most of the accepted signs of pulmonary eosinophilia have been reproduced in a well-known helminthologist in a self-inflicted experiment with the larvae of *B. pahangi* of the cat injected by mosquito bite (*Mansonia longipalpis*). Ten to fourteen weeks after infection, pulmonary symptoms and high eosinophilia were produced and eventually were cured by hetrazan, thus supporting Danaraj's hypothesis.

Tropical eosinophilia thus becomes an example of visceral "larva migrans" which is widely distributed.

The agent may also be the dog ascaris (*Toxocara canis*), but in some cases the cat (*T. cati*) may be involved. Infective-stage eggs, containing second stage larvae, are ingested by compatible hosts such as man or mouse. The eggs hatch in the upper levels of the small intestine and the freed larvae invade the intestinal wall, gain entrance to the mesenteric venules or lymphatics and are carried to the extra-intestinal viscera.

In the capillaries of the liver, less frequently the lungs, brain, eye or other viscera, the larvae are attacked by host-cell reaction of a granulomatous nature effectively blocking their further migration (Smith and Beaver, 1953). In the unnatural host these larvae do not grow or moult, but remain alive within the host cell capsule for weeks or months.

The larvae of *T. canis* are unable to complete their journeys via the lungs and back to the intestine and, at least those of this parasite, do not have an opportunity to mature in the human intestine. These results have recently been confirmed by veterinarians in the case of the pig ascaris introduced into mice, and more conclusively from the experiment of Chaudhuri and Saba (1959) who induced a volunteer to swallow 100 embryonated eggs of *T. canis*. A striking eosinophil response occurred on the 13th day. He suffered from an irritating cough and all signs of tropical eosinophilia were present.

Internal auto-infection of *Strongyloides stercoralis* is also thought to produce visceral larva migrans lesions.

It seems probable that tropical eosinophilia will eventually be regarded as an example of visceral larva migrans for the most by filariae of non-human origin.

Löffler's syndrome, originally described in Switzerland, is often mistaken for pulmonary tuberculosis (Freund and Samuelson, 1940). It resembles pulmonary coccidioidomycosis (see p. 594), to some extent sarcoidosis of the lung, and bronchial asthma associated with periarteritis nodosa.

Deschiens has shown that it is possible to distinguish between a parasitic and non-parasitic eosinophilia by giving cortisone or A.C.T.H. over a period of 1-2 weeks. In parasitic eosinophilia the number of eosinophiles in the blood remains stationary. (Thorn Test.)

An allied condition is *Eosinophilic erythredema*, a syndrome previously unknown, which occurred in Palestine (1945), where it has been described by Klopstock and Steinitz. It was characterized by the appearance of red swellings, infiltration of the skin and mucous membranes, which are transient and occur over wide areas, associated with an eosinophilic leucocytosis. It occurs at all ages and in both sexes and is obviously allergic in nature.

Section IX.—ANIMAL PARASITES AND ASSOCIATED DISEASES

CHAPTER XLIV

PARASITES OF THE CIRCULATORY SYSTEM : SCHISTOSOMIASIS (BILHARZIASIS)

Definition.—A group of diseases caused by certain digenetic trematodes of the family Schistosomidæ which inhabit the venous system of man in various tropical and subtropical countries.

I. GENITO-URINARY SCHISTOSOMIASIS (*Schistosoma hæmatobium*), or *Bilharziasis*

Synonyms.—Bilharziasis ; Bilharzia Disease ; Endemic Hæmaturia.

This parasite was originally found in man in Egypt by Bilharz in 1852, and subsequently by S. Cobbold in the Mangabey monkey (*Cercocebus fuliginosus*) in the London Zoo (1859).

Geographical distribution.—The eggs of this parasite were identified by Harley in Natal in 1864, and since then the disease has been found in other parts of Africa, more particularly along the eastern side of the continent, as far south as Port Elizabeth, and it is common throughout the Union of South Africa, especially in Natal. In Central Africa it occurs in the Northern Sudan, Uganda, the Congo, Rhodesia and in North Abyssinia ; it is met with in West Africa as well, especially in Liberia and Sierra Leone. In North Africa it is especially common in Morocco, Algeria, Tunis and Egypt. It also occurs in Arabia, parts of Palestine near Jaffa, S. Turkey and N. Syria (Cageaz river), Persia, Iraq, Cyprus, in the town of Tavira in Portugal, in Mauritius, Réunion, and Madagascar. An endemic focus of urinary schistosomiasis has been found at Gimvi in the Ratnagiri district of Bombay State by Gadgil and Shah (1952). The ova are terminal-spined and resemble those of *S. hæmatobium*. A few indigenous cases were reported, over fifty years ago, from Western Australia, where the infection had been introduced by soldiers returning from S. Africa. (Map X.)

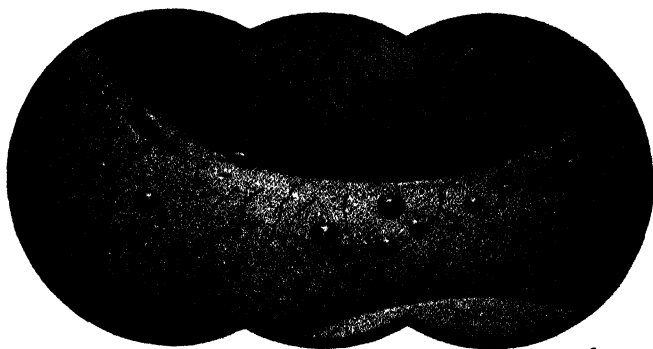
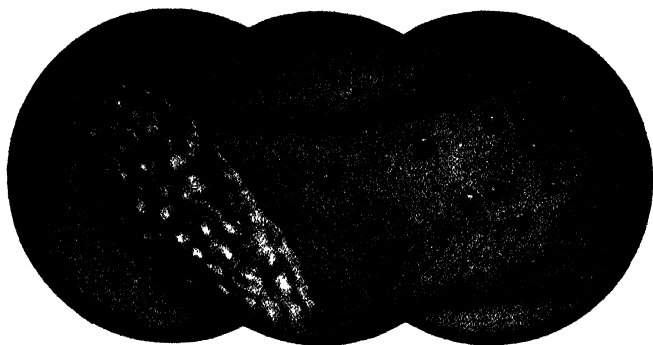
Precise information about the ravages of schistosomiasis in Egypt are forthcoming. Scott, as the result of 40,000 examinations, found that in the northern and eastern edge of the Delta, reaching as far as Cairo, 60 per cent. of the inhabitants are infected with *S. hæmatobium*, and an equal number with *S. mansoni* ; in the apical southern half of the Delta, however, though still 60 per cent. are infected with *S. hæmatobium*, only one-tenth of that number have *S. mansoni*. The line between the first and second areas is sharp and defined, and does not correspond to any noticeable topographic, hydrographic or demographic variation. Moreover, there appears to be no difference in the number of biomphalaria snails, the intermediary hosts of *S. mansoni*, in these two regions. In the northern two-thirds of that part of the Nile Valley between Cairo and Assiut, *S. hæmatobium* infects 50 per cent. of the population, but *S. mansoni* and

the biomphalaria snail are absent. In the southern third, where old *basin* irrigation—that is irrigation at flood Nile—takes the place of the new perennial irrigation, *S. hæmatobium* alone is present, but infects only 5 per cent. of the population. Heavy infection with *S. hæmatobium* is associated with perennial irrigation from high-level canals, which takes the place of flood irrigation, with alternate flushing and drying. In the district, where 5 per cent. of the inhabitants are infected with *S. hæmatobium*, 1 in 1,000 die from this infection: in the Northern Delta district, this proportion rises to 1 in 22.

Ætiology. *Parasite.*—*Schistosoma hæmatobium* (Fig. 299, A & B) is a unisexual trematode. The male measures 1–1.5 cm. in length by 1 mm. in breadth; its cylindrical appearance is due to the infolding of the two sides of the body to form a gynæcophoric canal. The female, darker, but longer, 2–2.5 cm. in length, is partially enclosed in the gynæcophoric canal of the male. Some parasites live in the blood of the portal vein and its mesenteric branches, but the majority dwell also in the pubic, vesical, and uterine plexuses.

The eggs are oval (Fig. 175), and are provided at one end with a definite spine. They measure 0.16 mm. by 0.06 mm. Normally they are voided in the urine, exceptionally in the fæces. It has been pointed out by Khalil that the hatching of the egg in water is due to osmotic pressure. A 0.75 per cent. salt solution completely inhibits this process. It has been generally supposed that the provision of a spine was designed to facilitate the passage of the egg through the blood-vessel wall, but probably, as Kohlschütter and Koppisch have pointed out, the spine merely facilitates the adherence of the ova to the wall. The ovum plays an entirely passive part, but the endothelial lining is the more active factor, followed by an inflammatory reaction which fixes it *in situ*. Only ova which are laid in blood vessels close the bladder pass to the outside, whilst all others are trapped in the tissues. (For further details regarding the life-history of this parasite, see p. 952.)

Pathology.—The changes brought about by this schistosome vary very much according to the degree and duration of the infection (Plate XX). In almost every case the walls of the urinary bladder are early affected. All that may be apparent to the naked eye at this stage is a certain amount of injection of the small vessels of the mucosa vesicæ, and certain exceedingly minute vesicular or papular elevations of the surface of this membrane. When these minute elevations are examined microscopically they are found to contain eggs, even in minute blood-vessels. Later, especially in the trigone of the bladder, there are rounded patches of inflammatory thickening which project somewhat, are granular on the surface, and dense; on section they creak under the knife as if they contained gritty particles. It is evident that these elevated, thickened patches are the result of an inflammatory process provoked by the clusters of eggs which the microscope reveals scattered throughout their entire extent. The eggs are principally deposited in the submucosa, less extensively in the mucous membrane, still less abundantly in the muscular walls of the organ or in its subserous connective tissue. They tend to occur in groups, each of which is invested with a connective-tissue capsule; or they may be lying in small blood-vessels which they occlude. Some eggs are seen to have undergone calcification; others are still fresh, either segmenting, or already containing a miracidium. On the surface of the rounded patches already mentioned, phosphatic deposits, also containing eggs, are not uncommon; from their yellow glistening appearance they are known as “sandy patches,” and sometimes they present minute sloughs. (Fig. 170.) Besides these indurated patches, various forms of polypoid excrescence—sometimes ulcerated—may protrude from the mucous surface into the cavity of the bladder. These various hyperplasiæ frequently contain the adult parasite as well as eggs. Ferguson and others described a nodular form



R.N. Lane

Bilharzial disease of the bladder before treatment, and one month after treatment with sodium antimony tartrate. The yellow nodules in Fig. 1 are the dead ova working their way through into the bladder cavity. They do not indicate active bilharzial disease.

(By permission of Brit. Journ. Surgery, Ogier Ward and Dr. J. B. Christopherson).

SCHISTOSOMIASIS OF THE BLADDER

PLATE XX

1

2

of schistosomiasis, an affection of the subperitoneal surface of the bladder, which closely resembles tuberculosis.

In addition to what may be designated the specific changes in the mucosa, the muscular coats of the bladder are generally hypertrophied. In consequence of this, as well as of the ingrowth of villosities and different forms of new growth, the capacity of the organ may be much diminished. Its mucous surface is generally coated with a sanguineous mucus containing myriads of eggs. Gravel or small stones—generally phosphatic—are sometimes found either embedded in lacunæ in the hypertrophied and roughened bladder-wall, or free in the cavity. Not infrequently a similar hyperplasia occurs in the ureters, and particularly



Fig. 170.—Section of bladder-wall, showing eggs of *Schistosoma hæmatobium* in tissues

towards their lower ends, even at an early stage. Gelfand and others have shown that often the lower third of the ureter is dilated with thickening of the walls. In rare instances the pelvis of the kidney is affected. Stricture of the ureter, both from small stones and from thickening of the mucous membrane, not infrequently results; this leads to dilatation of the pelvis and atrophy of the parenchyma of the kidney. It is easy to understand how, in time, these changes in the bladder and ureters may give rise to hydronephrosis, pyelitis, abscess of the kidney, and similar secondary affections. Hyperplasia of the prostate due to infiltration with eggs is sometimes found.

Hyperplasia from schistosomal infection may also occur in the vesiculæ seminales, penis, walls of the vagina, and cervix of the uterus, leading to corresponding bloody, egg-containing discharges. Thickening and papillomata of the female urethra, periurethral abscess, scarred and fibrous ovaries containing numbers of eggs, and lesions of the Fallopian tubes, mesosalpinx, and broad ligament have been reported. The body of the uterus is not usually affected, but eggs have been found in the endometrium. In the vagina the disease may be primary or an extension from the bladder. In the vulva papillomatous masses

closely resemble the confluent type of *condylomata lata* of syphilis, whilst the clitoris and external meatus may be destroyed and give rise to epithelioma of the vulva.

Schistosome eggs in small numbers have been found in the liver, in gallstones, in the heart, and in the kidneys, and occasionally in the brain, spinal cord, and lungs, conjunctiva and skin. Tumours of schistosomal origin have sometimes been met in connection with the peritoneum and ligaments of the uterus. The egg-production of *S. hæmatobium* is slower than that of *S. mansoni*. The schistosomes get to the lowest branches of the mesenteric veins, some even to the rectum, when eggs may appear in the fæces, but most migrate through the hæmorrhoidal vein to the venous plexus of the bladder. Gelfand has shown how they are distributed by arterio-venous anastomoses. When the eggs are deposited eosinophil cells are attracted and may produce micro-abscesses, forming pseudotubercles on the peritoneal surface of the bowel with resulting connective tissue. If they occur on mucous surfaces they take the form of small erosions or ulcers. Giant cells form and may completely absorb the egg.

The eggs can be conveniently demonstrated in the tissues by digesting selected portions in 3 per cent. potash solution.

Symptoms.—The symptoms produced by *S. hæmatobium* vary in degree within very wide limits. In the vast majority of cases the patient experiences no trouble whatever; in other instances suffering is very great. Indirectly, from the serious lesions of the urinary organs to which it may give rise, this schistosome is an occasional cause of death.

Early toxic symptoms, such as pyrexia with urticaria, have been noted, and may come on four weeks after exposure to infection. An interesting discovery is that of eggs of *S. hæmatobium* in skin papules, during the stage of invasion, on the lower chest, upper abdomen, scrotum and perineum (Black, 1945). The incubation period of definite disease varies from three months up to two and a half years. The cercariæ, on penetrating the skin, produce an irritative dermatitis as in other forms of schistosomiasis. (See p. 653.)

The most characteristic symptom of the presence of the parasite in the wall of the bladder is the passage of blood at the end of micturition, with or without a sense of urinary irritation. The quantity of blood passed and the degree of irritation are increased by exercise, by dietetic indiscretions, and by all such causes as are calculated to induce or aggravate cystitis. As a rule, it is only the last few drops of urine that contain blood; sometimes, however, the hæmorrhage is more extensive, and then the entire bulk of the urine may be blood-tinged. Occasionally, clots are passed.

If, in a case of moderate infection, the urine be passed into a glass and held up to the light, minute flocculi or coiled-up mucoid-looking threads will be seen floating about in the fluid. If it be allowed to stand, the flocculi, and perhaps minute blood-clots, will subside to the bottom of the vessel; these, on being taken up with a pipette and placed under the microscope, will be found to contain, besides blood-corpuscles and catarrhal products, large numbers of the characteristic terminal-spined eggs.

In doubtful cases, where eggs are few, the best way to find them is to get the patient to empty the bladder and to catch in a watch-glass the last few drops of urine which can be forced out by straining; these invariably contain eggs. A low power of the microscope suffices, and is best for diagnosis.

Pain is by no means always predominant; when it occurs it is generally a dull sense of oppression in the suprapubic region, deep-seated perineal pain, or scalding on micturition. Frequency of micturition is an early, and urgency a very common symptom. Rectal symptoms, with passage of blood and mucus, may co-exist with the urinary symptoms, and digital examination may detect ulceration above the prostatic lobes. This localized lesion may be due to *S. hæmatobium* alone, though mixed infections of *S. hæmatobium* and *S. mansoni* are very common, especially in the Nile Valley. Sometimes adult worms in copula are passed in the urine; this generally occurs after a copious hæmorrhage from a ruptured vessel. Gelfand and Barnett have described a peculiar form of retention with overflow and incontinence in the male African. There are three stages—a short period of progressively increasing difficulty in micturition with some retention, followed by complete retention with overflow for several days, and a final third stage in which the patient passes urine in increasing amounts till function is completely restored.

Hæmaturia lasts for months or years. In ordinary cases, provided no re-infection takes place, the hæmaturia tends to decrease, although eggs may continue for years to be found in the last few drops of urine passed. In severe cases, sooner or later, signs of cystitis supervene and give rise to a great deal of suffering. Not infrequently the eggs become the nuclei for stone, and symptoms of urinary

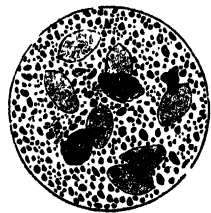


Fig. 171.—Section through nucleus of urinary calculus containing eggs of *S. hæmatobium*.

calculus are superadded (Fig. 171). Sometimes the pathological changes induced by the parasite in the bladder lead to new growth, in which event the symptoms become more urgent and the hæmaturia excessive. Hypertrophy, contraction, and even dilatation of the bladder are not unusual. Besides the bladder symptoms there may be signs of prostatic disease, or of disease of the vesiculæ, causing spermatorrhœa. In the latter case, eggs may be detected in the semen. In other instances the ureters and kidneys become involved, resulting in ureteric dilatation and hydronephrosis. Secondary infection of the urinary tract with septic cystitis commonly supervenes. From the suffering attending these aggravated forms of infection, the patients become anæmic, wasted, debilitated, and a ready prey to intercurrent disease.

Urinary fistulæ may occur anywhere in the neighbourhood of the genitals, but are especially common in the perineum and posterior surface of the scrotum, and originate from infiltration by eggs of the pubic tissue or roof of the urethra just in front of the bulb, the eggs of the parasite being deposited in the mucous or submucous tissue. Stricture of the urethra is by no means uncommon, especially when fistulæ are connected with the floor of the urethra. In the male, infiltration of the penile sheath may result in an elephantoid condition with chordee and actual obstruction to the urinary flow. (Fig. 172.)

Schistosomiasis of the cord and epididymis is by no means uncommon,

and is determined by the anatomical peculiarities of the anastomoses between the mesenteric and internal spermatic veins, and, it may be, between the pelvic venous plexuses and deferential veins. The tunica and testes are rarely affected. The onset is very gradual, and it occurs in young adults, whose attention is drawn to the swelling. The cord may be nodular and covered with lentil-like bodies, or it may be enveloped in a single big mass; the term "bilharzial rosary" well describes the condition. Cytoscopy, sigmoidoscopy, X-rays and complement-fixation tests may be needed for diagnosis, or to differentiate the lesions from somewhat similar

swellings due to filariasis, tuberculosis and syphilis. In massive infiltration, the testes may have to be removed; in the early stages medical treatment is effective.

The majority of infections of schistosomal disease of the spermatic cord are due to *S. hæmatobium*.

Charlewood and colleagues refer to the frequency and distribution of lesions due to *S. hæmatobium* in the pelvic organs of S. African women, whilst Gelfand in S. Rhodesia found that they are commonly associated with the eggs of *S. mansoni* in 30 cases: most commonly in the vagina, cervix, uterus, ovaries and less so in the Fallopian tubes. In the female urethra, according to Gilbert, the disease is an extension from the bladder with similar tissue changes producing thickening, ulceration of the mucous membrane and small papillomata which, emerging from



Fig. 172.—Urinary schistosomiasis: pseudo-elephantiasis of penis, due to infiltration by ova. (After Madden.)

the external meatus, may be mistaken for urethral caruncles. Periurethral abscesses may also form. Although the uterus is not usually affected, fibrosis of the ovaries and occlusion of the Fallopian tubes are common, so it is small wonder that in the female this disease causes sterility.

Vaginitis and cervicitis are also produced by this parasite. Papillary growths and ulcers may be mistaken for carcinoma. On the vulva, papillomatous masses containing schistosome eggs are common. Similar excrescences about the anus, in the groin and perineum can be distinguished from venereal warts by microscopical examination.

Pulmonary schistosomiasis (Egyptian Ayerza's disease).—In 103 cases of urinary and intestinal schistosomiasis diagnosed in Cairo 49 pulmonary complications were revealed. The first grade consists of focal arterial changes: the second of widespread arterial with slight cardiac changes: the third widespread arterial changes with gross heart involvement. It is necessary to associate these changes with both species of schistosomes; as Kenawy has pointed out, the ova of both cause a similar arteritis of the pulmonary arterioles, but in the case of *S. mansoni* this is invariably associated with hepatic cirrhosis. This widespread obliteration of the pulmonary arterioles at times produces a marked rise of blood pressure, hypertrophy of the right ventricle, and finally right heart

failure. It is stressed that cyanosis only makes its appearance as a terminal event and that secondary lung infections are complications.

The predominating symptom in pulmonary schistosomiasis is dyspnoea, together with other signs of pulmonary hypertension, which show themselves by palpitations and præcordial pain. It differs from other forms of cardiopathy in the absence of polyglobulins.

The X-ray appearances are distinctive and show what is known as the bilharzial *cor pulmonale*, enlargement of the right side of the heart with the shape of mitral configuration. There may also be a triangular shadow in the right hilum due to enlargement of the right branch of the pulmonary artery. There is often a diffuse and fine mottling of the lungs, due to bilharzial tubercles, which resemble miliary tuberculosis.

Schistosome eggs are rarely to be found in the sputum, but according to Pyjper this is more easily effected if a twenty-four hour specimen of sputum is digested for one hour in an equal quantity of 4 per cent. K.O.H. and then centrifuged.

Eggs have been found also in the brain and spinal cord, thus accounting for epileptic and paralytic symptoms from which the patients had suffered, but these supervene only in hyper-infected individuals. One case of schistosome myelitis was described by Day and Kenawy, with the customary symptoms. At autopsy eggs of *S. hæmatobium* were demonstrated in the lumbar enlargement of the cord.

Eye.—Schistosomal lesions of the conjunctiva have now been described by Badir (1946). This interesting condition appears to be rare. The majority were suffering from urinary symptoms as well. Swellings of the palpebral conjunctiva of the upper lid, yellowish pink masses between the inner margin of the limbus and the semilunar fold extending upward into the fornix have been described. The most curious feature was the discovery of the adult worms lying in a dilated vein (branch of the superior ophthalmic vein) in the region of the caruncle. Eggs of *S. hæmatobium* have been found in granuloma of the conjunctiva. It is an open question how the adult parasites reach the conjunctival tissues.

Throat.—Shahkeen in Egypt reported the case of a man with an obstructive tumour above the vocal cords. Biopsy specimens showed vascular fibrous tissue in which were embedded fresh calcified ova of *S. hæmatobium*.

Lip.—Khalil (1954) has described an ulcer of the lip which had been diagnosed clinically as syphilitic. In the granulomatous base fresh and calcified schistosome ova were demonstrated.

Chesterman found certain districts in the Congo where eggs which appeared at first to be *S. hæmatobium* are found only in the faeces, giving rise to dysenteric symptoms closely resembling those produced by *S. mansoni*, but in this instance they are longer and with more attenuated extremities than those usually seen in the urine (see Appendix, p. 956). Similar conditions have been recorded from the Assiut district of Egypt, where only *S. hæmatobium* is present.

Fisher, at the instigation of Chesterman, brought forward a considerable amount of evidence that this Congo schistosomiasis is not due to *S. hæmatobium* as was thought, but to *S. intercalatum*, a species which in its morphology is intermediate between that of *S. hæmatobium* and *S. bovis*. The spindle-shaped eggs resemble those of the latter species and also of *S. matthei*, with terminal well-developed spine, which may attain a length of 20 μ . The intermediary host appears to be *Physopsis africana*. Zellweger found this species commonly in

Gaboon, along the course of the Ogowé river and its tributaries. This discovery has been confirmed by Schwetz.

The *symptoms* produced by *S. intercalatum* appear to be mild; in Yakusu (Congo) it has been found that 50 per cent. of the school-children are infected; their health is not seriously affected, but sometimes spleen and liver are enlarged. Dysenteric symptoms and abdominal pain constitute the only outward signs of the disease, and pulmonary manifestations (in contrast to *S. hæmatobium*) are practically absent. Toxic manifestations, which usually accompany massive infections with *S. mansoni*, or *S. japonicum*, have been noted. (Fig. 173.) The hepatic and intestinal symptoms run a similar course, with urticaria and bronchial asthma. The infected bowel, as seen by sigmoidoscopic examination, has a granular appearance suggesting sandpaper, and there are petechiæ of minute size, but no polypi or ulcers.



Fig. 173.—Schistosomiasis of the Congo with splenomegaly. (Dr. C. C. Chesterman.)

Sequelæ.—Schistosomal appendicitis, due to accumulation of *S. hæmatobium* eggs in the appendix, is a clinical entity. Lovett Campbell, in Northern Nigeria, found them in 57 per cent. of all appendices removed at operation, and considers that this infection may produce symptoms requiring urgent surgical intervention. Barsoum, on the other hand, stated that it does not cause or predispose to appendicitis of the inflammatory type.

Carcinoma.—In Egypt there is a wide belief that vesical schistosomiasis is the primary cause of cancer of the bladder which has become the most common form of malignant disease, especially amongst male agricultural workers. Halawam and Samami recommend cytodiagnosis and the recognition of cancer cells in the urine as the most practical method of making the diagnosis.

Diagnosis.—The diagnosis of this disease is not difficult; the presence of eggs in the urine is decisive (Figs. 174, 175, 176). In countries like Egypt, where the disease must often concur with chyluria, with stone, with vesical tumour, with gonorrhœal cystitis, and with pyelitis, as well as with prostatic disease, care must be exercised in each particular case to separate the special factors to which the various symptoms are attributable. Thus, in chyluria with schistosomal disease, there will be chyle in the urine in addition to blood. In such a combination the clot which forms will be larger, will contain oil granules, globules, and very probably microfilariae, in addition to schistosome eggs. Stone in the bladder, when suspected, has to be sought with the sound. Difficulty may sometimes arise when eggs are scanty, or have ceased altogether to come away in consequence of the death of the parent worms. Snips of tissue taken from the bladder or rectum are digested in 10 per cent. potash and examined for eggs (Gelfand and Ross). Since the introduction of rectal biopsy it has been

found that in a large proportion of cases *S. hæmatobium*, eggs can be demonstrated in the rectal mucosa as well. The use of the *miriadiascope* may be of considerable assistance. This consists of a specially constructed wooden rack painted dull black to hold centrifuge tubes and a hand lens 1 in. in diameter and of 2½ in. focal length which gives sufficient magnification to view the miracidia swimming about in the water. The value of this instrument is two-fold.

(1) The procedure is relatively simple and an opinion as to the presence of schistosomiasis can be given in an out-station clinic or even during school inspection.

(2) It is employed in determining the viability of schistosome ova.



Fig. 174.—*Schistosoma hæmatobium* eggs in urine, showing contained miracidia. (Dr. H. K. Giffen.)

For use the terminal portion of the urine is collected and stood for 30 minutes after which the upper part is decanted, leaving sufficient to fill a centrifuge tube. This is centrifuged at low speed and the liquid is gently drawn off; 5 ml. of water are added to the deposit. The tube is then inserted into one of the holes provided in the rack. Hatching is usually complete within 20 minutes but may be delayed up to 40. If viable ova are present in the urine they hatch and the miracidia can be seen swimming around actively (Meeser, Ross and Blair, 1949).

The mischief wrought by the parasite remains, although the eggs—the most certain evidence of the parasite's previous presence—may no longer be discharged. But, even if the eggs are very few, they may still be found

in the last drop or two of urine passed. If they are not found in the urine, sometimes, by scratching the surface of the bladder with a sound and examining the shreds of mucus so obtained, a few, calcified it may be, but presenting the characteristic spine, may be seen with the microscope. Confirmatory evidence may be obtained from the pus cells, the majority of which are eosinophils. By examining urine sediments with the addition of water in a special rack with each tube at 40° to the horizontal, Meeser and colleagues have shown that the hatching miracidia from eggs may be observed with a hand lens. Tubes of urine are spun in a centrifuge at low speed and water is added to correspond with the apertures in the rack, but must not contain any injurious substance. The miracidia stand out shiny and bright against the dull background. Fifteen minutes is allowed for hatching and the number of miracidia varies. An average infection shows 10-20 per tube. Further evidence may be obtained by the tests described below.

The following reactions are common to all species of schistosoma.

Complement-fixation.—Fairley in 1917 described a complement-deviation test employing as antigen an extract of the livers of infected snails (*Biomphalaria boissyi*). This antigen is prepared by macerating a number of livers containing cercariæ of *S. mansoni* in absolute alcohol, filtering, and evaporating by means of a Sprengel's pump. A saline extract is then made of the dried residue and its anti-complementary dose estimated. The general technique is the same as for the quantitative Wassermann reaction in syphilis. Alves and Blair have improved the antigen and avoided false positive reactions by preparing an extract of cercariæ.

The reaction is apparently a group reaction, in so far as an antigen prepared from cercariæ of *S. mansoni* will give positive results with *S. hæmatobium* serum in 89 per cent. of early cases and also with that of *S. spindale*. Further, Bettencourt and Borges stated that similar reactions take place with *Fasciola hepatica* antigen. A positive result may be obtained in early infections even before the appearance of eggs in the dejecta. It is not so specific in the later as in the earlier stages, but may be employed as a check to treatment.

Coutinho (1952) has prepared an antigen from the adult flukes by washing them in physiological saline and distilled water, drawing it off, and adding acetone to 10 times the volume of the worms; on shaking the supernatant fluid is at first opalescent, but later becomes transparent. It is then decanted, and at 37° C. for half an hour the acetone is evaporated. The worms are then triturated to a fine powder which is extracted in a water bath at 56° C. (in Coca's solution, 1 per cent. suspension) for half an hour. Schofield (1959) has proved that, using antigen prepared from naturally-infected snail (*S. spindale*, for example), it will retain the potency for 30 years. In cases of less than 3 years' duration the test is a valuable diagnostic aid, but in those of longer duration it is unreliable.

Intradermal reaction.—Fairley elaborated an intradermal test, similar to the Casoni reaction in hydatid. A saline extract of dried livers, 0.5 per cent., of *Biomphalaria exusta* infected with *S. spindale* of the goat, is used. The extract, having been rendered bacteria-free by passage through a filter, is injected intradermally in a dose of 4 min. A positive reaction is given by an immediate wheal and a zone of erythema with outrunners, and a delayed type of reaction in from five to eighteen hours. This test is useful as a means of diagnosis in all forms of schistosomiasis, but remains positive for years after the patient has been

cured. The results have been improved by using the cercarial antigen of Alves and Blair.¹ The measurement of the wheal is twice the size of the control.

Cercarial reaction.—Living schistosome cercariæ, when placed in serum from men and animals recently suffering from schistosomiasis, develop a close-fitting transparent membrane which differs from the loose precipitate which collects around similar cercariæ in normal human or animal serum (Alves). Vogel and Minning describe the same phenomenon as "Cercarial Hüllen reaction" (C.H.R.), and believe that the test may be used as an aid to diagnosis. A cercarial agglutination test with sera of infected humans and animals is now being employed by Lui and Bang (1950) and Oliver-Gonzalez (1955).

As a further aid Senterfit finds that miracidia of *S. mansoni*, when added to the inactivated serum of infected hamsters or monkeys, become immobilized, whereas, when exposed to normal sera, they are unaffected. The same holds good for *S. hæmatobium*. It is considered that both C.H.R. and miracidial immobilization test (M.I.T.) are sensitive *in vitro* techniques for the detection of antibody sera

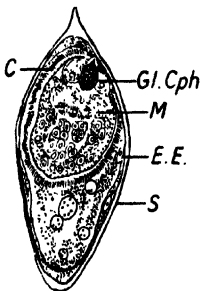


Fig. 175. — Egg of *S. hæmatobium* to show development of miracidium.

S., shell; *E.E.*, embryonic envelope; *M.*, miracidium; *C.*, cilia; *Gl. Cph.*, oesophageal glands.



Fig. 176. — Egg of *Schistosoma hæmatobium*, showing changes produced in contained miracidium by antimony tartrate.

(Dr. John Anderson.)

in experimental animals. However, cross reactions with cercariæ of different genera of schistosomes indicate that there is little specificity within this family. The circumoval precipitin test of Oliver-Gonzalez is being used. Precipitins from adult living eggs incubated in sera of infected humans at 37° C. for 24 hours.

Cystoscopic examination.—In the early stages of the localized disease (within two months of infection) the cystoscope reveals sparse grey discrete elevations in the trigone around the ureteric orifices; later, definite hæmorrhagic papules appear with surrounding inflammation. Later still, characteristic "sandy patches," resembling ridges of sea-sand, with papillomata, can be distinguished. (Plate XX.) These appearances are pathognomonic.

Prognosis.—The long life of the parasite, which may be thirty-five years or even more, is serious. Another important element in prognosis

¹ The technique is rather elaborate, and consists of collecting the cercariæ from one infected snail on filter paper, which is subsequently stored in carbol saline in the refrigerator.

is the degree of infection: the greater the number of parasites, the more severe and the more extensive is the disease they produce. As with filarial infection, the greater the number of cases in a district, the greater the proportionate probability of severe infections. The prognosis is practically that of a chronic cystitis depending on a remediable, and not in itself fatal, cause. Much suffering may often be produced, and, as a consequence, anæmia and debility. Possibly calculus may be formed; possibly grave renal disease may ensue; possibly, eventually, villous or epitheliomatous growths in the bladder. In the milder degrees of infection which fortunately are the commonest, the patient seems to be in no way inconvenienced by the parasite, and generally escapes all serious consequences. In any case, mild or severe, there may be attacks of hæmaturia from time to time; as a rule, the quantity of blood thereby lost is insignificant.

TREATMENT

I. Tartar Emetic (Sodium antimonyl tartrate).—Intravenous injections are given on alternate days over a period of four to six weeks. It is customary to commence with $\frac{1}{2}$ gr. of tartar emetic dissolved in 10 ml. of freshly-distilled sterile water, and gradually to increase the amount by $\frac{1}{2}$ gr. until the maximum individual dose of 2–2½ gr. is reached. It is not always necessary to dilute the antimony with 10 ml. of water; for amounts under 1 gr., 6 ml. suffices. Some toxic phenomena may be avoided by dissolving in 5 per cent. glucose solution, but it should not be boiled for any length of time nor subjected to pressure. For large numbers of patients stock solution of tartar emetic is made up in a sterilized vaccine bottle with a rubber cap in a strength of $\frac{1}{2}$ gr. to 1 ml. of distilled water; this can be further diluted later. The solution should be drawn into a syringe of 10 ml. capacity, and slowly injected into the median basilic or cephalic vein. The total amount injected to kill all adult schistosomes is about 25–30 gr. of tartar emetic. Rapid improvement in the condition of the urine should soon be observed; generally all traces of blood disappear after the injection of 15 gr. For children a total of 10 gr. appears to be sufficient, the maximum individual dose being 1 gr. This course of treatment, once commenced, should be persisted in; cases almost invariably relapse if there are interruptions.

An intensive method of treatment with sodium antimonyl tartrate was introduced by Alves and Blair (1946), with the idea of concentrating the amount of antimony in the shortest period of time, in 100 cases. This method has not been universally successful, and has been subjected to criticism as being too dangerous. The total dosage was 12 mg. per kilo—or 1 gr. to 12 lb. Thus an individual weighing 144 lb. receives 12 gr.

Potassium antimonyl tartrate may also be used.

II. Anthiomaline (*Lithium antimony thiomalate*) is recommended as a more efficacious drug than tartar emetic. There are no contra-indications; intramuscular injections are not painful, and there is no evidence of either local or general reactions. Anthiomaline is very soluble and contains 16 per cent. of antimony. It is supplied in 2 ml. ampoules of a 6 per cent. solution containing 0.02 grm. of antimony. The initial dose is 0.5 ml. for a child of twelve and 1.5 ml. for others. The maximum individual dose for an adult is 4 ml.; for a child of twelve 2 ml.; and the total dosage is about 65 ml. It is best given by the intravenous route on alternate days.

III. Fouadin (*Neocantimosan, stibophen*).—A trivalent compound containing 13 per cent. of antimony was introduced in 1929 for the treatment of schistosomiasis in Egypt. It is claimed that a cure may be effected in nineteen days, in

contradistinction to the more prolonged tartar-emetic treatment. The drug is given *intramuscularly* in 7 per cent. solution and is put up in ampoules. The dosage is as follows:

For an adult :	1st day	1.5 ml.
	2nd "	3.5 "
	3rd "	5 "

Subsequently 5 ml. on alternate days up to the 15th.

The total number of injections should be from ten to fifteen, totalling 0.4 gm. of antimony. Of this quantity 50 per cent. is excreted in the urine and 4 per cent. in the faeces. Late vomiting occurs in 2.5 per cent. of the cases. There is apparently no local reaction except, occasionally, spasms of coughing. The urine is examined after the last injection, and if living eggs are still present, further injections are indicated.

Fouadin should not be given *intravenously*, but should be administered *intramuscularly* on alternate days. In over 300 school-children treated in this manner no toxic symptoms were observed. Overdosage must be avoided. One of the most serious and permanent injuries is retrobulbar neuritis with central scotoma and loss of colour sense.

Occasionally sulphohæmoglobinuria develops during treatment with stibophen. The symptoms are those of severe shock with intravascular hæmolysis. The spectroscopic examination of the urine for the bands of sulphohæmoglobin is diagnostic.

IV. Trivalent sodium antimony tartrate (*Solustibosan*, *trivalent SG*).—

This is a compound which can be administered by either intravenous or intramuscular injection. Sterilization by heat is inadvisable. For *S. hæmatobium* infections it is given intravenously in doses of 180 mgm. daily for six days. The solution is 6 per cent. and the amount injected 3 ml.

Side-effects are notably absent. The total amount of antimony injected is 408 mgm. compared with 566 mgm. in the case of fouadin.

V. "T.W. Sb." (*Friedheim*) is *antimony dimercapto-potassium-succinate* and is a water-soluble trivalent organic antimonial bound to sulphur atoms of vicinal dithiols to form pentatonic rings. It has been in use since 1954 and can be given intramuscularly in 5 per cent. glucose and is much less toxic than tartar emetic. The dose is 0.2–0.5 gm. intravenously, or intramuscularly, for six days and is safe and effective. Total dosage is 2–3 gm. Its main action is to block egg deposition. No side-effects have been observed, except salivation. Alves (1958) has reported good results from injections of 0.5 gm. for 3 days and now proposes to reduce the course to 2 days. Therefore it promises to be an ideal drug for mass prophylaxis. It is agreed that it is more efficacious for *S. hæmatobium*.

VI. *Miracil D* (*Leucanthone*, *Nilodin*) was shown to have definite therapeutic activity by Kikuth and Goennert for mice and monkeys infected with *S. mansoni*, and by Vogel for animals infected with *S. hæmatobium*. Monkeys tolerate 200 mgm. per kg. four times a week. The first effect is to cause the parasites to retreat from the mesenteric veins. In man it is given by mouth and is readily absorbed in doses of 0.2–0.3 gm. daily. Overdosage produces insomnia, nausea and prostration and sometimes yellow skin discoloration. The great advantage of this compound is that it can be given by the mouth, but, when tested out in African and European schoolboys in Southern Rhodesia, the results were at first doubtful. Now Watson, Abdel Azim and colleagues have obtained better results in Egypt (1948). When higher and more frequent doses were given the results were better. In their most recent series doses up to 300 mgm., at twelve hour intervals, were

given as long as fourteen days. In *S. hæmatobium* infections viable ova disappeared from the urine; in *S. mansoni* cases eggs vanished from the fæces. The physical condition improved, but most relapsed later. The best results are achieved by keeping the blood miracid D up to the lethal level, by administration every twelve hours.

In Rhodesia high cure rates are reported with this drug. The total dose is calculated to 60 mgm. per kgm., two daily for three days. Each tablet is 0.5 gm. A child of 6-10 should receive 1 tablet in the morning, another in the evening on the first day, the same on the second, followed by half a tablet morning and evening of the third day; the total dose being 2.5 gm. For a child aged between 10-14 the total dose is 3 gm., the patient receiving 1 tablet morning and evening every day for 3 days. A young adult is given 1½ tablets the first morning, followed by 1 tablet the same evening, and 1 tablet morning and evening in each of the two subsequent days, the total being 3.25 gm. A heavy adult is given a total dose of 5.5 gm., receiving 2 tablets morning and evening each of the 2 days and the third morning, and 1 tablet on the third evening. (Alves and Blair, 1949, 1950).

This drug cures about 60 per cent. and exerts a specific action on the urinal schistosome (*S. hæmatobium*).

The following dosage is recommended :

Weight of Patient.	Total Dosage.	3-day Course.	6-day Course.
kg. 20 lbs. 44	1200 mgm.	Daily dose 400 mgm.	Daily dose 200 mgm.
" 40 lbs. 88	2400 mgm.	" " 800 mgm.	" " 400 mgm.
" 80 lbs. 176	4800 mgm.	" " 1600 mgm.	" " 800 mgm.

TABLE X.—DOSAGE OF ANTIMONY COMPOUNDS

Compound.	Percentage of Antimony.	Total Dosage.
Ant. potass. tart.	36	1.9 gm.
Ant. sodii. tart.	39.5	1.6 gm.
Fouadin.	13.5	60-65 ml.
Anthiomaline.	16	50-65 ml.

A new preparation (1959) M & B 2948, a *para-amino-phenoxy-1-phthaliamido-5-pentane*, tested out by Schneider in French Guinea, in tablets by the mouth of 120-370 mgm. per kgm. cures 50 per cent. of *S. hæmatobium* cases in courses of 5 days. For children the total dose varies from 6-29 gm.

Local measures.—Stone and troublesome new growths are removed by operation. Mackie and others reported good results from perineal cystotomy and drainage when distress is extreme. Perineal fistula must be dealt with on ordinary surgical principles. Hyperplasia of the vagina and cervix is best treated by scraping. If, by care, re-infection from water can be avoided, there is no need to send the patient away.

Prophylaxis.—Most of the general measures detailed here are applicable to the other forms of human schistosomiasis. They resolve themselves into (1) the protection of snail habitats from fouling and infections; (2) destruction of snail populations; (3) avoidance of cercarial infection. The first measures are not easily applied, but the advantages are obvious, especially by education and propaganda, which has met with

considerable success in the Sudan. The sanitary measures comprise the siting of all villages at least 300 metres from snail-infested canals, which are fenced around, and the provision of good wells and latrines near the villages.

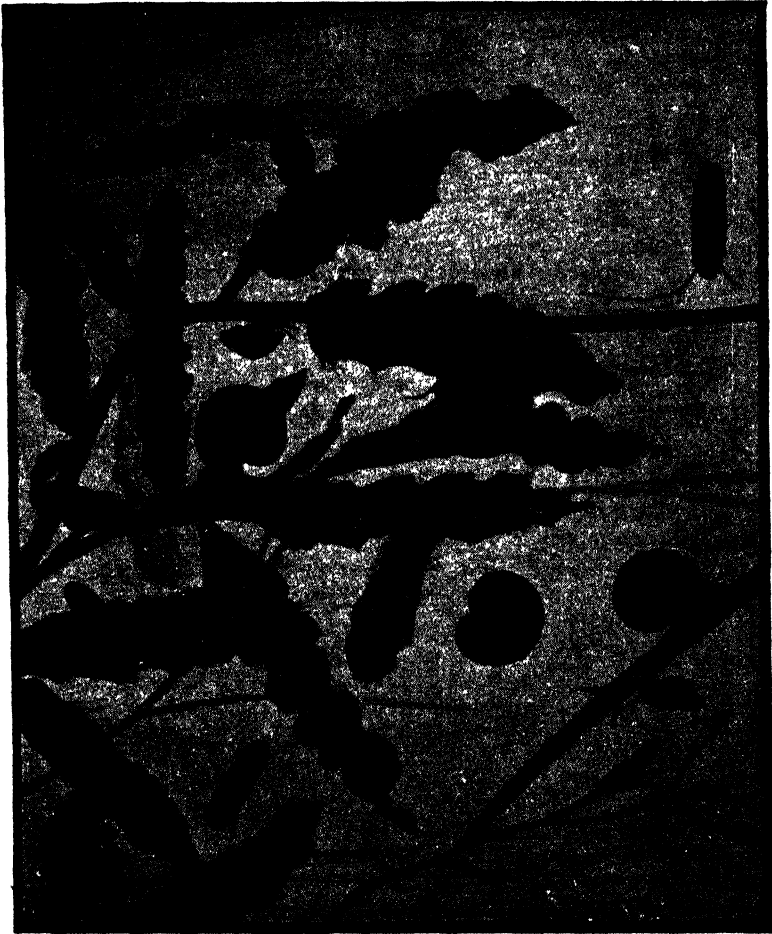


Fig. 177.—The intermediary hosts of *S. hæmatobium* and *S. mansoni* (*Biomphalaria boissayi* and *Bulinus contortus*) in their natural surroundings. Nat. size. (J. K. Lund, del.)

The second consists of killing or eliminating the snail intermediaries. These comprise the introduction of chemicals, the removal of snails by manual labour, the removal of aquatic vegetation and other elements necessary for their environment, biological control by introduction, or encouragement, of natural enemies, or unsuitable types of vegetation,

reconstruction of natural water-courses, flushing and draining of such water-courses. The chemicals employed are copper sulphate, copper carbonate, ammonium sulphate, slaked lime and sodium pentachlorophenate.

The efficacy of drying up the canals, ponds and watercourses, which was advocated originally by Leiper, is doubtful for *Bulinus truncatus* cannot be exterminated by emptying and drying the canals for 40 days. Even in pools in oases miles removed from the Nile and main channels these snails reappear miraculously, directly they fill up after rains. Probably the eggs are reintroduced on the feet of ducks and other water birds, but Barlow has shown that the chief species of snails can withstand desiccation for one year at least. Thus Zakaria (1955), in a study of *Bulinus truncatus* in Baghdad, found the snail density of a stretch of 10 km. of a canal had 58 million. Rapid desiccation caused a high mortality, but in canals which were emptied the snails were found to have buried to a depth of 1-8 cm. and only succumbed when the mud had dried out.

In the endemic districts, children, in particular, should be carefully and repeatedly warned, by school and religious teachers, against drinking or bathing in rivers, ponds, and canals. (Fig. 177.) Sportsmen should be warned against wading, especially when shooting snipe, in localities known to be infected; even fishing in fresh-water canals in countries like Egypt is not free from risk. Swamps, when slightly brackish, are safe. Drinking-water should be boiled, and every care must be exercised to prevent the diffusion of the disease by prohibiting the evacuation of excreta into or near water, where the miracidia might find the opportunity of development and transmission. This prohibition should not be restricted to patients exhibiting definite symptoms of the disease, but extended to all, because, as special inquiries have shown, a large proportion of the infected do not suffer from any troublesome symptom and are often unaware of their infection.

Ransford in the Kota Kota district of Nyasaland has shown that the leaves of a shrub—*Tephrosia vogelii*—which is easily cultivated—acts as an efficient molluscicide in a strength of 1 : 4,000. It is commonly used by the native population as a fish poison, but is harmless to human beings and animals. Deschiens and Lamy have discovered a small ostracod, *Cypindopsis hartwigi*, which feeds on the snails, *Bulinus* and *Biomphalaria*, and destroys them in the laboratory.

Sodium pentachlorophenate (*Santobrite*) appears to be the most practical compound for flowing water, killing snails at 10 p.p.m. Halawani has commented upon the molluscicidal activity of sodium pentachlorophenate and *dinitro-o-cyclo-hexylphenol* (DCHP) under field conditions. In stagnant canals and drains only a proportion of snails were killed in 24 hours by sodium pentachlorophenate and DCHP at 5 and 10 parts per million, but after 3 days all were dead and no live ones were recovered after a period of 2 months. Experiments showed that snails were killed within one hour at the site of application, but as a rule the current carried the molluscicide away and stopped its action.

The third measure—avoidance of cercarial infection—is more practical. It consists of avoidance of skin contact with or drinking of infected water. It has been shown experimentally that cercariae only penetrate the skin when water is evaporating—hence vigorous wiping with a towel after bathing is a useful method of prophylaxis. Cercaricidal substances are employed. Originally Witenberg and

Goffe found chloramine more effective than gaseous chlorine or sodium hypochlorite. The concentration necessary is 0.22 parts per million residual after ten minutes' application for chloramine, 0.42 for sodium hypochlorite and 0.6 for gaseous chlorine. The heat of the direct rays of the sun is lethal to cercariæ. DDT has been found to possess slight anticercarial action.

It has been noted in pools in S. Africa which had been sprayed with DDT from the air that there is a rise in the snail population, and therefore increases the chance of infection with schistosomes. In a search for potent molluscides von Brand and his associates have found only two of any value—pentabromophenol and pentachlorophenol—but both are extreme irritants to the mucous membrane of the respiratory tract.

Protective ointment.—This measure was developed by the U.S. Army for protecting soldiers in the Far East and it applies to all three forms of schistosomiasis. It is not suitable for swimmers but for fishermen and those running exceptional risks. The ointment is rubbed on those parts exposed to infection, such as hands, forearms, ankles and feet.

It is composed as follows:

Castor oil	40 parts
Lanoline	15 parts
Diglycol stearate	10 parts
Dibutyl phthalate	25 parts
Paraffin wax	10 parts

It is recommended by Alves in S. Rhodesia (1958).

Mass treatments.—The efficacy of prevention in any anti-schistosomal scheme is greatly enhanced by concurrent treatment of the infected population.

II. INTESTINAL SCHISTOSOMIASIS (*Schistosoma mansoni*)

Synonym.—Intestinal bilharziasis ; Schistosomal dysentery.

Epidemiology and geographical distribution.—*Schistosoma mansoni* requires slightly different conditions for its propagation from those of *S. hæmatobium*, so that, though frequently found associated in Africa, yet there are areas in the Southern Sudan and in West Africa where *S. mansoni* is prevalent and *S. hæmatobium* absent. Although schistosomiasis occurs in eleven out of fourteen provinces in the Sudan, *S. hæmatobium* is the common type in the north, and south of the Upper Nile Province *S. mansoni* alone is found. (Map XI.) *S. mansoni* is spreading rapidly throughout Central Africa, owing to the development of irrigation, hydro-electric installations and in the building of dams. During the last 30 years it has become established in S. Rhodesia and has become a menace, though as yet, only one-third as common as *S. hæmatobium*. It is now found in Portuguese E. Africa and is nearing the borders of the S. African Union. It has a patchy distribution in contrast to the widespread occurrence of *S. hæmatobium*.

Infection is acquired during the months of the year when water is sufficiently shallow to permit a high concentration of cercariæ. In inland lakes the seasonal incidence is from October to the end of January, but in the Nile backwaters the danger period is usually February to June.

In South America, especially in Surinam and Venezuela, *S. mansoni* is widespread ; in the latter country it forms an important problem, and 80,000 are infected in one area, the central part of the Northern coastal range where the intermediary, *Biomphalaria glabrata*,¹ is found. Infesta-

¹ Formerly *Planorbis guadeloupensis*.

tion is commonest where sugar cane is irrigated. In several communities at least one quarter are infected, especially men. Whenever snails occur near houses the women are as highly infected as men, and the children acquire infestation early. The West African green monkey (*Cercopithecus sabæus*) constitutes a reservoir of *S. mansoni* infection in W. Africa, and also in St. Kitts in the Lesser Antilles where it now lives in a feral state. In Kenya recently the dog-faced baboon (*Papio doguera*) has been found to constitute a reservoir of infection, and in W. Africa the Guinea baboon (*Papio papio*) Miller (1960).

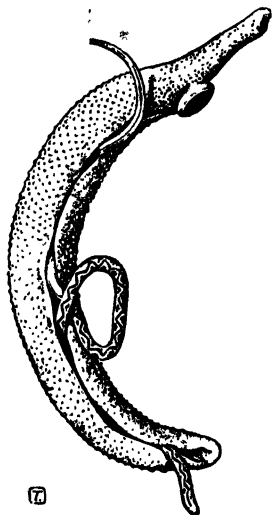


Fig. 178.—*Schistosoma mansoni*, male and female $\times 6$. (After Looss.)

Ætiology.—The parasite much resembles *S. hæmatobium*. The distinguishing features are that it is generally smaller and more grossly tuberculated. There are other points (Fig. 178). The female deposits one or two eggs at a time—a circumstance perhaps explicable by the peculiar structure of the uterus. The eggs are somewhat spindle-shaped, provided with a lateral spine (Plate XXVII, 12, facing p. 1096) and are generally slightly shorter than those of *S. hæmatobium*, 0.15 mm. in length by 0.06 mm. in diameter. These eggs are passed out in the fæces, rarely in the urine, and hatch out a ciliated miracidium. (See also p. 697.) Cases of urinary schistosomiasis have been described by Cowan (1958) and Gelfand, caused by combined *S. mansoni* and *S. hæmatobium* with eggs of both species in the urine in the absence of any intestinal involvement. This species may live in man for 26 years. In S. America the peccary is very susceptible to infection (Torrealba, 1959).

Pathology of intestinal schistosomiasis.—The eggs of *S. mansoni* may be found in great numbers in the liver, where they give rise to a peculiar form of "clay pipe-stem" cirrhosis of Symmers and also Budd-Chiari Syndrome (*endophlebitis obliterans hepatica*). Sandy patches, due to effete calcified eggs, cover large areas of the intestinal surface, and may give rise to acute choleraic diarrhoea. Black pigment granules are deposited in the interstitial and secreting cells of the liver, and have been shown in both *S. mansoni* and *S. hæmatobium* infections, but are commoner and more abundant in the former. It is golden brown or sepia, and gives the same reactions as malarial pigment (hæmatin). The gall bladder has very rarely been found infected. The lymph-glands in the retro-peritoneal tissue are enlarged. There is generally an appreciable hypertrophy of the spleen, which may possibly be attributed to toxic absorption and which gives rise to the clinical syndrome known as Egyptian splenomegaly.

The affections of the colon may be classified into four types—(a) those with simple thickening of the mucous membrane; (b) thickening of the mucosa with papillomata and ulcers; (c) pericolic tumours associated with papillomata; (d) polypi of the cæcum which may lead to intussusception. Infiltration of the appendix with *S. mansoni* eggs is not uncommon and may give rise to the

signs and symptoms of acute appendicitis, which is complicated by secondary bacterial infection (Fig. 179).

The small intestine is hardly ever affected, except in its lower part. In the colon the disease causes the formation of septic foci, and ulceration of the bowel-wall appears to be produced by the tearing-off of pedunculated papillomata by the peristaltic action of the intestine. By this means, and by sloughing at the base, are produced clear-cut ulcers which may become subsequently infected with *Entamoeba histolytica*. Perforation of the bowel may occur. Fairley and Lampe drew attention to the similarity of the disseminated pericolic nodules to miliary tuberculosis and also to infiltration of the mesenteric glands by schistosome eggs. Disseminated bilharzial tumours of the peritoneum closely resemble carcinomatosis (Trim). It is an anomaly that *S. mansoni* eggs are frequently obtained in scrapings made from the bladder mucosa, though they are rarely found in the urine.

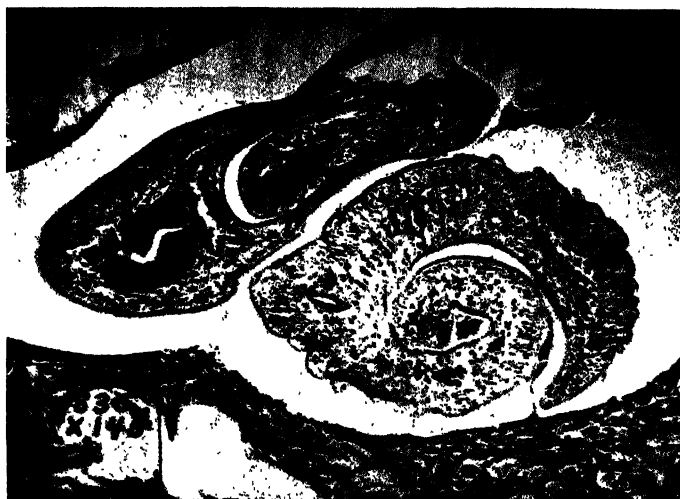


Fig. 179.—Male and female *S. mansoni* in rectal polyp. (Dr. H. K. Giffen.)

Shaw and Ghareeb emphasized the importance of pulmonary damage, *cor pulmonale*, as the cause of death in *S. mansoni* as well as in *S. hæmatobium* infections. Diffuse arterial changes resembling Ayerza's disease are produced. Parenchymatous tubercles are found containing the characteristic eggs. In some 10 per cent. of cases, the adult worms have been found in the pulmonary veins. This complication appears to be rare in Brazil where Meira and colleagues have described a few isolated cases.

VISCERAL SCHISTOSOMIASIS ; HEPATO-LIENAL FIBROSIS ; EGYPTIAN SPLENOMEGALY

Splenomegaly, associated with cirrhosis of the liver, is common in all parts of Upper and Lower Egypt, where 20 per cent. of infants under four years of age are found to have splenic enlargement and anæmia. It is common among the working class at all ages up to thirty ; in the young it is apt to run a severe course, while at a later age the chronic form, progressing to ascites, is met. In children the disease is generally associated with rickets:

in adults with ancylostomiasis. A similar syndrome was recorded by Dye from Northern Nyasaland in patients also infected with *Schistosoma mansoni*. Hyperplasia of the spleen appears to be secondary to hepatic cirrhosis, and to this condition are to be ascribed the anæmia and leucopenia which are found in advanced cases. Those with advanced cirrhosis are just those who have few intestinal symptoms, and who pass scanty, or,*it may be, no eggs in the stools. To account for this anomaly it has been suggested that in these cases unisexual infestation with a preponderance of male worms exists.



Fig. 180.—Rectal schistosomiasis adenomata prolapsed through anus. (After Madden.)

Eggs of *S. mansoni* may be found on digestion of solid organs, such as the liver and spleen, with potash. This form of schistosomiasis is rare in South America.

Pathology of hepato-lienal form (Egyptian splenomegaly).—Ferguson recorded that the average weight of the spleen is 30 oz.; it may reach 300 oz., and, according to Day, may contain scanty eggs of *S. mansoni*. It is firm; microscopically there is a general hyperplasia with active phagocytosis of red cells by macrophages.

Onsystated that the only certain method of finding eggs in these spleens is by macerating the tissues in 20 per cent. soda solution and then centrifugalizing. The eggs are phagocytosed by giant cells, a process accompanied by considerable

eosinophilia. In order to account for the widespread nature of the visceral lesions and the paucity of eggs, the view was put forward by Girges and others that, Egyptian splenomegaly is caused by infection by male *Schistosoma mansoni*, in the absence of the female; but this view is not widely held. On the other hand the presence of "spinster" females has been reported.

Abdel Shafi claimed that, although the incidence of eggs in the liver is fairly high, yet other organs and tissues show much heavier deposits, that infection of the liver alone is unknown, and that the number of eggs in the liver substance is small in comparison with the extensive cirrhotic changes in that organ.

The liver is usually enlarged in the early stages, and presents the picture of early multilobular cirrhosis with isolated necrotic foci. In the more advanced stages the organ is shrunken and firmly fixed to the diaphragm by adhesions. There is a comparative absence of bile-duct formation. The bone-marrow shows no great disturbance of the hæmopoietic system.

Polak (1959) has studied the various changes in the liver by laparoscopy and needle biopsy. By these means granulomata are revealed and pipestem cirrhosis of Symmers as well as the coarse periportal fibrosis of Hashem. Fibrotic changes are also seen in the spleen and, rarely, eggs of the parasite.

Symptoms of intestinal schistosomiasis.—The earliest manifestations are associated with the entry of the cercariæ into the skin, and consist of an irritative dermatitis depending upon the intensity of exposure.

Within a few hours minute petechiæ may be observed at the sites of invasion of blood vessels, but these disappear in a day or two.

S. mansoni inhabits chiefly the branches of the portal vein in the liver and the mesenteric veins. Its eggs, deposited within the submucous layer of the large intestine, give rise to dysentery-like symptoms, commencing six to eight weeks after infection; mucus with blood is passed from time to time, the egg-laden stools becoming frequent and their passage being perhaps attended with tenesmus. In certain well-established cases small (sometimes large) branching, soft growths are felt inside the sphincter ani. (Fig. 180.) They resemble polypoid growths and are apt to be mistaken for internal piles. It has been remarked that, though common in Egypt and S.^W America they have not been encountered in *S. Rhodesia* (Morris). Small, shotty, pink or violet papules with a red aerola may occur on external genitalia and perineum. They are separate, or in groups, and tend to appear in crops. They may extend as high up the bowel as the sigmoid flexure. If one of these growths is teased up, the lateral-spined eggs are seen in the debris.

In heavy infections, in early cases, toxic symptoms resembling those of Katayama disease (p. 717) are noted, especially in Europeans. General symptoms consist of intermittent pyrexia, with giant urticaria, abdominal pain, anorexia, rigors, and pulmonary symptoms. (Chart 27.) The very evident urticaria, often accompanied by swelling of the face and lips, is thought by some to be due to destruction of cercariæ in the skin capillaries; by others to the filtering out of foreign proteins from the portal circulation. Ritchken and Gelfand have described this toxæmic stage as seen in *S. Rhodesia*. They find that sometimes many months may elapse between the entry of schistosome larvæ in the body and the development of acute symptoms. The Katayama syndrome is usually seen in children in a small proportion. Pyrexia may last several days, more usually it is spasmodic. In some there is tenderness of the liver, loss of weight, urticarial

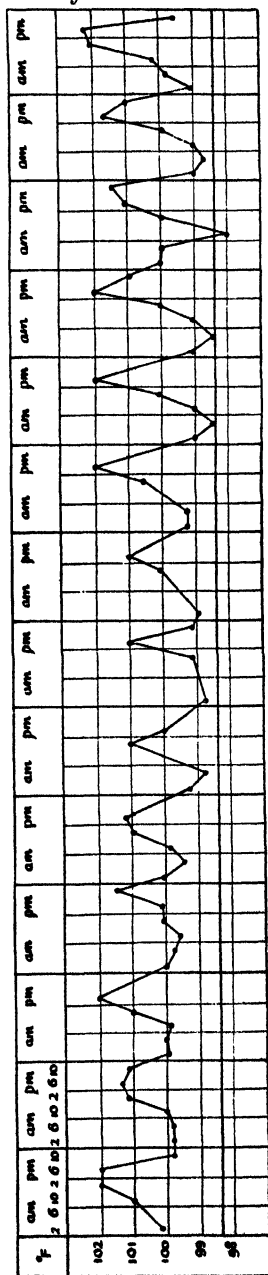


Chart 27.—Four-hourly temperature chart of acute schistosomiasis (*S. mansoni*). (Lawton.)

eruptions and, finally, splenomegaly. Miliary lesions in the lung can be demonstrated by radiology. The extra-urinary and extra-intestinal phenomena are due to embolism of ova from these sources. It is unlikely that the pulmonary symptoms are due to cercariæ trapped in lung capillaries, most likely they are due to allergy. Pons stated that cough is invariably present in early cases, and tenderness is found over the liver, spleen, and intestines,

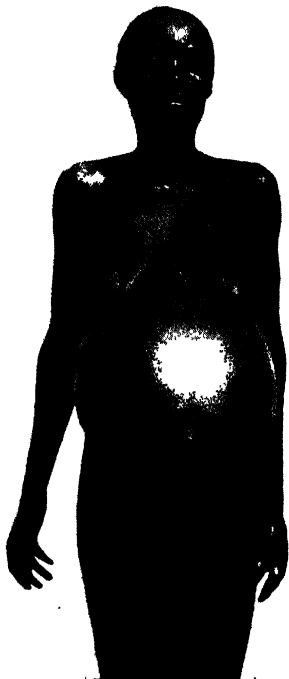


Fig. 181. — Egyptian splenomegaly.
(Dr. S. C. Jones.)

especially over the cæcum. On abdominal examination of dysenteriform cases enlargement of liver as well as of spleen is frequently found. A pronounced leucocytosis with high eosinophilia (up to 76 per cent.) is invariable.

Later, localized symptoms, with passage of dysenteric motions, supervene.

In the terminal stages large palpable abdominal tumours may form, and intestinal stasis or distension may take place. Infiltration of the buttocks with eggs, leading to induration and fistulæ, is not uncommon. When the liver has become markedly cirrhotic, ascites may be present. Pneumonia from egg-deposition in the lungs is an occasional complication. Pulmonary sclerosis, resembling Ayerza's disease, appears to be comparatively common (Erfan, 1948).

Sometimes dysenteric attacks may develop into acute diarrhœa, of choleraic type, which may prove fatal. Deposition of the eggs in the appendix occurs comparatively often and produces symptoms of a sub-

acute appendicitis. Generally, the organ is much thickened and infiltrated so that it can easily be palpated. The diagnosis of schistosomal appendicitis from septic or amœbic appendicitis may be difficult. Chronic intestinal obstruction may result from schistosomal tumours and may be accompanied by serious peritonitis (Trim).

Symptoms of the hepato-lienal form (Egyptian splenomegaly).

The symptoms of this condition, appear to be more objective than subjective. There are irregular fever, wasting, and a striking pallor. The spleen is obviously enlarged, hard and firm, often reaching to the umbilicus (Fig. 181); the liver also in the early stages is enlarged. Vomiting and diarrhœa are frequent. In the later stages œdemas, of varying degree, and purpuric rashes may ensue. The fever is generally irregular, inter-

mittent, and not amenable to quinine or other antimalarials. The splenic enlargement causes pain and discomfort, especially after meals, and on exertion gives rise to a dragging sensation, though the main symptoms are caused by debility and anæmia. As the disease progresses, so pyrexia increases, until the steady enlargement of the liver and spleen causes the costal angle to expand. Hæmatemesis often occurs, but jaundice is rare. Hepatic abscess associated with visceral schistosomiasis has been reported by Graham. The final stage is ushered in by cirrhotic changes in the liver, which becomes hard and firm and shrinks within the costal margin. The spleen also becomes fibrotic, but does not proportionately decrease in size.



Fig. 182.—Microphotograph of miracidium of *Schistosoma mansoni* escaping from egg. $\times 1,500$. (Dr. A. J. Chalmers.)

The pain, which is due to perisplenitis and perihepatic adhesions, increases, while vomiting is common. Finally, the patient succumbs with symptoms of hepatic cirrhosis, ascites, and emaciation. Fatal hæmatemeses are reported by Willard (1956) in Puerto Rico from extensive periportal fibrosis causing hæmorrhages from gastric varices. Death is usually due to pulmonary complications.

Kenawy described a continuous venous hum which may be heard by the stethoscope over the liver. Unfortunately, this sign is of no great assistance in differential diagnosis, for a similar sound has been noted in other forms of cirrhosis, as well as in Banti's disease.

The blood picture varies. In the early stages there is a leucocytosis of 17,000 and myelocytes may be present; later, progressive anæmia of the microcytic type becomes apparent, with leucopenia of 8,000 and a mononuclear increase of 10-17 per cent.

Among the rarer complications, thrombosis of the portal vein and hepatic carcinoma have been recorded.

The course of the disease is generally protracted: in older children and adults it may run twenty years or more. Ascites is always regarded as unfavourable. In all its aspects this stage resembles that of schistosomiasis japonica.

Diagnosis.—The characteristic eggs are easily found in the faeces under low powers of the microscope; they may be very scanty, and it is necessary to examine three or more specimens before arriving at a negative diagnosis. (Fig. 182.) They are more easily found in solid than in fluid stools, especially in the outer portions of a motion. Quite a high proportion of cases are latent—that is to say, they do not present any recognizable or urgent symptoms. Examination of mucus and scrapings from the rectal mucosa, obtained through the proctoscope or sigmoidoscope is usually more reliable than faeces examination. The importance of rectal mucosal snips in diagnosis has been emphasized, but scrape preparations with a Volkmann spoon are equally satisfactory and cause less disturbance. The material should be placed directly under the microscope without the addition of saline or any other diluent.

Rectal biopsy was practised by Ottolina and Atencio in 1942 when they noticed at necropsy that the greatest numbers of eggs were to be found in the upper half of the rectal ampulla. Since then this method has been used, when faecal examinations have been negative. The comparative value of stool examinations and rectal biopsy has been investigated by Spingarn who examined 187 with *mansoni* infection and found ova in 93 per cent. by biopsy and 83 per cent. by faeces examination. They attribute the superiority of biopsy to the concentration of ova in the upper half of the rectal ampulla. Crypt-aspiration by special suction apparatus has been practised by American specialists.

Fülleborn recommended the Telemann method of finding the eggs when scanty. The faeces are shaken up with a mixture of concentrated hydrochloric acid, 1 part, water, 1 part, ether, 2 parts, and strained through gauze; the filtrate is centrifuged and examined. The deposit may then be mixed with water and the eggs encouraged to hatch, when the miracidia are more easily detected (*see* p. 697).

In this form of schistosomiasis the total serum proteins do not vary much from normal, but the globulin and globulin-albumin rates and the percentage of euglobulin are increased, more especially in patients with splenomegaly (Khalil and Hassan). The formaldehyde test may, therefore, constitute a reliable means of differentiation from leishmaniasis.

The complement-fixation and intradermal tests are the same as in *S. haematobium* infections (p. 698). Pifano and Maver have recorded good results in Venezuela with alcoholic extracts of the hepato-pancreas of infected *Biomphalaria glabrata*; more recently with extracts made from adult *S. mansoni* which give 95 per cent. of positive reactions. In the stage of invasion antibodies appear at the beginning of the third week. Standen has devised a special technique for concentrating cercariae of *S. mansoni* for the preparation of antigen. Hunter and Ritchie (1958) state that neither the cercarial antigens nor the alcoholic fraction from the adults

give as good results as the saline extract, preserved with merthiolate (1 = 7,500) of which 0.01–0.1 ml. is injected intradermally. False positives occur in 4–5 per cent.

Pifano and Pedrique (1957) have found the "Cercarienhüllen" reaction of Vogel (*see* p. 699), or cercaria-sheathing reaction, very helpful. In a large series this reaction was positive in 78 per cent., and on this basis it is strongly recommended that this method should be employed in routine diagnosis.

In rectal disease, should *S. mansoni* be suspected, an adenomatous growth may be removed by forceps and examined for eggs.

Sigmoidoscopic examination usually reveals pedunculated adenopapillomata in the upper part of the rectum, but usually this is unnecessary, as they can be felt by digital examination and may sometimes be seen protruding in polypoid masses from the anus. In very early cases granular patches can be detected on the rectal mucosa from which eggs may be obtained. The localized thickenings of the large intestine, due to polypi and pericolic growths in the transverse and pelvic colons, may be palpated in heavily infected subjects.

Differential diagnosis of the hepato-lienal form has to be made from splenic anæmia and other forms of splenomegaly. Injections of adrenalin decrease the size of the spleen in splenic anæmia, but are without effect in schistosomiasis.

TREATMENT

Gross changes in the organs are more extensive than in *S. hæmatobium* infections, due partly to toxic absorption and partly to deposition of eggs. Hence, it may prove necessary to remove polypoid or adenomatous growths obstructing the intestines. In early cases antimony is as successful as it is in *S. hæmatobium* infections. The course of treatment is the same, but, on the whole, the end results are less satisfactory and it may be necessary to give more than one course. Reactions may be due to the toxins liberated by disintegrating worms. For this phenergan, 25 mgm. three times daily, is advocated. Persistent vomiting or jaundice are indications that the treatment should be stopped. Intravenous solustibosan has given better results. Miracil D (*Nilodin*) has so far proved unsatisfactory.

T.W. Sb. (Friedheim) (*see* p. 867).—Recent reports on this compound for *S. mansoni* infections vary considerably. Alves considers that it is much more effective than other antimonials, but Pitchford and Harrison (1959) have not had such good results so far.¹ The compound 6171 R.P. (M & B 2948A) in doses by the mouth of 260–560 mgm. per kgm. according to Schneider, caused the disappearance of viable eggs in 57 per cent. of cases. Gastric phenomena can be avoided by giving the drug in capsules.

Operative treatment of intestinal schistosomiasis.—Dolbey and Fahmy held that the rational method of obtaining a permanent cure in cases with extensive disease of the rectum is excision of the whole tube of mucous membrane. Lengths of 12–15 in. can be removed with ease. A circular incision is made at the junction of skin and anal mucous membrane; the external sphincter and levator ani attachment are separated by blunt dissection; when once the latter has been separated, the mucous tube may

¹Davis (1960), in Kenya, found egg-production impaired for 2–4 weeks after a single intramuscular injection.

be loosened by the gloved finger and withdrawn until the upper limit of the papillomata is reached. Recovery is uneventful; there is little tendency to retraction of the tube, and control of the anal sphincter is regained. This operation is unsuitable for very anæmic or debilitated patients.

Operative treatment of the hepato-lienal form.—According to Richards, palliative operative interferences, such as frequent tapping and the Talma-Morrison operation (omentopexy), are permissible in cases with ascites, though in early cases before the development of ascites, he performed splenectomy with success. Coleman, Bateman and Stiven confirmed the value of this operation. The mortality-rate is about 15 per cent. and deaths are due to late shock. Great care is still necessary in the selection and preparation of cases for operation. Ascites, pellagra, heart disease and debility are contra-indications. Considerable leucocytosis differentiates this condition from leukæmia. In his account of 890 cases, Stiven stated that five to six weeks' preliminary treatment is necessary; it should consist of tetrachlor ethylene, to get rid of intestinal parasites, and intravenous injections of neosalvarsan for syphilis. The weight of the spleens removed by this surgeon averaged $3\frac{1}{2}$ lb. The favourable results appear to be permanent, and ascites does not develop. Day claimed that early cases are curable with tartar emetic.

Observations made in Egypt upon the late results of splenectomy have been summarized by Abdou and Grace. Of 35 operated during a period of ten years 30 were alive. Of the five fatal cases, one died of portal thrombosis. The general results were considered good. The lassitude and anæmia disappeared; nutrition was restored and health maintained. In Pernambuco, Brazil, da Silva operated upon some sixty during $6\frac{1}{2}$ years. Maximum incidence was between 15–24 years. Hæmatemesis due to rupture of œsophageal veins occurred in 56.6 per cent., and this constituted an indication for operation. Pre-operative antimony treatment is not advised. There were 15 post-operative deaths.

The constant expulsion of ova from the tissues indicates a vital process as the ovum is still alive and secretes a substance which creates a passage for its exit.

Criterion of cure.—It is essential that a standard of cure for schistosomiasis should be accepted. Friedheim (1954) has pointed out that the presence of dead ova in the excreta does not preclude the presence of living worms in the body, but merely indicates that the deposition of ova is seriously impaired.

It is also stated that the dead ova passed after the course of antimony treatment may still be due to living worms. A successful cure therefore means that the subject ceases to pass living or dead ova by the end of the third week after the last injection. On the other hand Blair and others maintain that a cure should be judged by the absence of viable ova when at least three hatching-out tests for miracidia in the fæces or urine are negative (see Appendix, p. 1108). Absence of viable ova from the excreta for three months has been suggested as a reasonable period to estimate a cure, but most are agreed that Christopherson's estimate is correct, that the minimum follow-up time should be one year. Gelfand believes that a

cure can be assumed when, for all practical purposes, *all ova* have disappeared after an interval of six weeks. There are other difficulties connected with this subject. It is pointed out that often in *S. haematobium* infections terminal-spined ova are found in the urine, and rarely in the faeces despite the fact that large numbers are present in a mucosal rectal snip taken from the rectum.

Immunity.—Vogel, investigating serological and immunological aspects, found that a slowly built-up immunity takes place in both *S. mansoni* and *S. japonicum* infections. He exposed rhesus monkeys at monthly intervals to infection with 25 cercariae each. Under these conditions the number of eggs excreted by these monkeys at first increased steadily, but after 6–9 months it began to fall, in spite of superinfection. Finally the egg output ceased almost completely and at this time exposure of the monkeys to doses of cercariae, which would have proved fatal in uninfected monkeys, was without effect. At autopsy live stunted adult schistosomes of both sexes were present.

Prognosis.—This is the same as for *S. haematobium*, but it must be remembered that this disease is generally latent, and that even large intestinal polypi may give rise to little or no inconvenience.

Cases with papillomata of the rectum, dysenteric symptoms, tenesmus, and anaemia, and those with actual obstruction of the intestinal canal and cirrhotic changes in the liver, must be regarded as serious.

Prophylaxis is the same as in *S. haematobium* (p. 702). There appears to be a greater probability of contracting the disease in the neighbourhood of canals and waterways, which are the favourite haunt of *Biomphalaria boissyi*, of which a high proportion (50 per cent. or more in some cases) are found to be infected with the cercariae of this trematode in Egypt. In Northern Nigeria and in Kenya, infection has been recorded from bathing in clear pools in the absence of any obvious aquatic vegetation. In South America and Venezuela prophylaxis is concerned mainly with avoiding collections of water and cane-field irrigation canals which form the haunts of *Biomphalaria glabrata*.

To sterilize water for washing and drinking purposes the Katadyne process is recommended. This is a colloidal silica compound which is fitted inside the filter candle.

In Pernambuco (Brazil), slaked lime has been found effective against *Biomphalaria glabrata* and *B. (Planorbis) centimetralis*. Chlorination of 0·2 parts per million kill cercariae of *S. mansoni* in 30 minutes. Strong electric light induces activity and shortens lifespan, whilst ultra-violet and direct sunlight are both fatal. Extremes of pH outside the 4·6–10 range are fatal and cercariae are rapidly killed in a 1·5 per cent. sodium chloride solution.

Berry and others have found that *santobrite*, sodium pentachlorophenate and copper pentachlorophenate are excellent and their cost reasonable. At 9·5 ppm. calculated at a 6-hour flow-rate this mixture destroyed all snails for a distance of 1·5 miles downstream (*see* p. 704).

Temperature is one of the most important environmental factors determining the efficacy of molluscicides. In Egypt the monthly average water temperature in canals may show a seasonal variation of 18° C.

They suggest that molluscicides should be applied during the hot summer months when they are most efficient.

In addition to the predators mentioned on p. 704, several species of crayfish have been found to feed on eggs and larval stages of the snail hosts of *S. mansoni*. Various kinds of fish, tested in aquaria feed on freshwater snails. An American species is *Umbra pygmaea* and in S. America there is *Cichlasoma biocellatum*. Dias (1954) discovered that cultures of *Bacillus pinottii* were lethal to various species of *Planorbis* and *Biomphalaria*, especially to *Biomphalaria glabrata*. When tried out under field conditions in 1955 with cultures of this organism in peptone water the tests were fairly successful. In Venezuela Torrealba and associates (1958), finding that papaya fruit contains a principle which is toxic to snails, prepared a watery solution which kills *B. glabrata* in a strength of 1:20,000. The toxic principle is contained in the epimesocarp of *Sapindus saponaria*.

III. EASTERN SCHISTOSOMIASIS (*Schistosoma japonicum*)

Synonym.—Katayama Disease. Bilharziasis japonica.

Geographical distribution.—For very many years an endemic disease characterized by splenomegaly, enlargement of the liver, cachexia, ascites, pyrexia, and dysenteric symptoms had been observed in Japan. In 1888 Majima found eggs in a cirrhotic liver, and in 1904 Katsurada saw a miracidium emerge from similar eggs which he had found in faeces; later, he discovered the adult trematode, *S. japonicum*, in the portal veins of the cat. In that year also Catto found similar parasites in a Chinaman in Singapore. The next addition to knowledge was made by Katsurada, who succeeded in communicating the parasite to cats by immersing their legs in the water of certain ponds reputed to convey the disease. In 1913 Miyairi and Suzuki traced the parasite, through snails common in the infected districts, back to the vertebrate host, a discovery confirmed in the following year by Leiper and Atkinson.

The parasite had been found principally in Chinese and Japanese, though a few Europeans—mostly naval officers and sportsmen, addicted to snipe-shooting in the rice-fields—had acquired the disease. Its present range, as far as is known, may be stated as follows: In China it occurs in endemic foci in the Yangtze basin on both banks from Ichang, 350 miles above Hankow, to the sea; in the provinces of Hunan (Siang River), Hupeh, Anhwei, Kiangsu and Kiangsi. An endemic centre has been reported from Shiuchow, on the North River near Canton, and also from Foochow (Fukien). It has been recorded on the Burmese border between Yunnan and the Northern Shan States. In Japan it is especially prevalent in the province of Hiroshima and in the village of Katayama. Five schistosomiasis endemic areas are known in Japan. The most important extends along the Tone river to N. and E. of Tokio, an extensive rice-growing area. Endemic foci also exist in Southern Formosa, and in the Southern Philippine Islands—Samar, Leyte, Mindanao and in Celebes (Indonesia). Several hundred cases were discovered in American troops within a limited period in October, 1944, during the invasion of Layte. (Map X). In countries where it exists, pigs, dogs, cats, rats, buffaloes and imported cattle and horses are found naturally infected: native cows, on the other hand, appear to be immune.

Etiology.—The parasite closely resembles *S. haematobium*, though it is smaller and the integument is smooth and non-tuberculated. In proportion, the acetabulum or ventral sucker is longer and stouter than in either *S. haematobium*

or *S. mansoni*. The eggs, smooth and slightly oval, measure 0.08 mm. by 0.06 mm., and pass through the intestines into the fæces. They possess a rudimentary lateral spine, and show considerable variation in size, but in the uterus of the female schistosomus they are much smaller than those in the fæces. (See p. 1100.) Vogel (1942) has shown that the egg passes through three stages—immature, mature, and degenerate. New laid eggs require 10 days to develop to maturity, The miracidium can live the same period within the egg. In man this parasite can live from 20–25 years.

Hsu (1954) in Formosa has shown that a biological species of *S. japonicum* exists which infests domestic animals, especially pigs.

The miracidium, after casting its cilia, develops in fresh-water molluscs of the genus *Oncomelania*¹, Gredler, 1881, which have a widespread distribution in Japan and China; probably all species of this genus are potential carriers of *S. japonicum*.

Pathology.—The outstanding feature is the great enlargement of the liver and spleen. The former is hypertrophied and nodular, due to the formation and contraction of fibrous tissue; on digesting with 3 per cent. potash solution, it is found to contain many eggs. The great enlargement of the spleen, on the other hand, is probably due to absorption of toxins or, possibly, to back-pressure, as eggs are seldom found there. As in other forms of schistosomiasis, granules of black pigment are found in both viscera. The appendices epiploicæ are greatly thickened and may be matted together; the mesenteric and retro-peritoneal lymph-glands are enlarged; hypertrophy and thickening of the lower parts of the intestinal tract, with formation of ulcers and polypoid growths filled with eggs, are generally noted. The bladder is unaffected.

Occasionally, indurations of the pia mater and granulomatous lesions of the cerebral cortex have been found, eggs being present in great numbers. The young forms of the parasite enter the general circulation through the veins and collect in the lungs, apparently entering the liver by traversing the mediastinum and the diaphragm. Inside the portal system they soon reach maturity. Infection of the fœtus during intra-uterine life is apparently possible.

Symptoms.—The disease produced by *S. japonicum* is serious and, when pronounced, sooner or later proves fatal. The gravity of any given case depends, amongst other things, on the degree of infection and the circumstances of the patient. Of 1,077 persons near Shushima, Japan, examined by Koiki, 42 were found infected. Of these, only 22 were not in good health. Penetration of the skin by the cercariæ causes an intense pruritus, partly mechanical, and partly due to an irritating substance secreted by the larvæ. The erythema thus produced was formerly regarded by the Japanese as a skin disease, "kabure," and is similar to that of the two other forms of schistosomiasis.

The course of the disease can be divided into three stages: *invasion*, *deposition* and *fibrosis*. The first (Katayama disease) occurs shortly after infection and lasts about a month. It is associated with toxic symptoms—pyrexia, giant urticaria, abdominal pain, paroxysmal cough, leucocytosis and a high eosinophilia (60 per cent. or more). Dermatographia and angioneurotic oedema are common. As in the case of *S. hæmatobium*, eggs have been found in multiple skin lesions by Fishbon (1946) in American soldiers in Leyte. The lesions consisted of pruritic papules in chest and

¹ There has been much confusion about the correct nomenclature of these snails; the reader is referred to Appendix, p. 963.

scrotum. Biopsies showed inflammatory reaction with eosinophile cells surrounding distorted schistosome ova. Garcia found eggs in biopsy of chronic ulcer on the leg of a child of ten. Some early infections are

accompanied by marked anorexia and sometimes with diarrhoea. The

second is characterized by great emaciation and is accompanied by dysenteric symptoms and enlargement of liver and spleen. Abdominal pain in right hypochondrium is severe. A well-developed cough and mild pulmonary changes are common. Sometimes typhoidal symptoms supervene. These are just the cases

which respond to intravenous potassium antimony tartrate. Some develop temporary pulmonary lesions resembling those reported in other schistosome infections. These peculiar pulmonary changes are believed to arise from fresh dissemination of ova to the lungs or to some allergic manifestations. The *third* or final stage, when it does supervene, occurs from three to five years after infection. In this the liver and spleen are cirrhotic and enlarged (hepatolienal fibrosis). Ascites and œdema of the extremities appear, with anæmia and exacerbations of dysenteric symptoms (Fig. 183). Superficial collateral veins are distended and prominent. Varicose oesophageal veins can often be demonstrated radiologically, but hæmorrhage is infrequent. A similar liver fibrosis with ascites and portal hypertension with great enlargement of the spleen are seen in older children, associated with dwarfism and retardation of sexual development. The patient may die of exhaustion, of some terminal infection, or of Jacksonian fits or hemiplegia. *S. japonicum* eggs tend to be localized in the brain and C.N.S. Total blindness, owing to deposition of eggs in the cerebral



Fig. 183.—Terminal stages of Eastern schistosomiasis. (Photograph by Dr. J. A. Thomson ; by courtesy of Wellcome Bur. Sci. Res.)

cortex, or destruction of the visual centres may ensue.

Faust and Wright, reporting on the outbreak amongst American

troops in Leyte in early cases, recognized a fulminating type, a severe type with sudden onset, an insidious type and quite numerous asymptomatic cases. In the severe forms a relatively common symptom was "nuchal rigidity." A complication supervening in the chronic form is cæco-colic intussusception. The ileum may be invaginated into the ascending colon. Marked leucocytosis and eosinophilia are associated with the first two stages.

Cheng and others (1957) have drawn attention to involvement of the intestinal tract, such as pyloric obstruction due to schistosomal granuloma resembling carcinoma and to fistula of the sigmoid resembling a tuberculous lesion.

Recent observations in China suggest that the greater part of the people infected in youth gradually overcome the infection, though they continue to be exposed to it. Experimental evidence, obtained from superinfection in monkeys, leads to the conviction that a similar resistance can be acquired by man.

A recent development has been the recognition of a selective hypopituitarism in schistosomal hypophyseal dwarfism by Cheng and Chao-Ling (1959).

These people, mostly males, average about 18 years. There is impairment of gonad function, with sexual immaturity and deranged carbohydrate metabolism. X-ray examination has shown subcalcification of bone and other changes already described by other Chinese workers.

Diagnosis.—All cases of urticarial fever from the endemic districts should be watched for many months (especially if eosinophilia persists after the subsidence of the primary attack) and the stools examined for eggs of *S. japonicum*. All cases of chronic intestinal disturbance from the districts mentioned, especially if associated with enlargement of liver and spleen, should be regarded as possible cases of schistosomiasis, and the blood and stools should be examined. If the characteristic eggs (Fig. 184) are discovered definite diagnosis is established. Fæces concentration methods for demonstration of eggs are frequently necessary. Frequent stool examinations disclose an increasing number of infections. In a series of 980 in which consecutive stools were examined, 480 were found positive after the first and 750 by the seventh. A series of 5,000 hatching techniques (see p. 1108) disclosed 1,500 more positives than sedimentation techniques.

Complement-fixation reactions and intradermal tests, as in *S. hematobium* infection, can be carried out with antigen made from cercariæ of *S. spindale* of the Indian water buffalo. Williams has shown that the antigen remains effective in sealed ampoules for eighteen years. A similar reaction is obtained with extracts from the bodies of the adult trematodes when the serum of artificially-infected horses is used (Seuzas, 1917). Most has employed intradermal tests with antigens made from adult schistosomes and found them specific. Pesigan

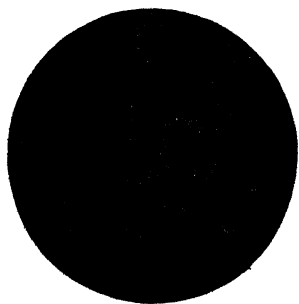


Fig. 184.—Eggs of *S. japonicum* in faeces. $\times 250$. (Microphotograph by Dr. J. Bell.)

(1950), using cercarial antigen prepared by method of Alves and Blair, concluded that the resulting wheal should be measured at intervals of 5, 10, 20, and 30 minutes after intradermal injection. According to Faust and Meleney the aldehyde or serum-globulin test is strongly positive in many cases.

"Liver ova" antigen is the most reliable. Rabbits infected with cercariæ are killed 6-10 weeks later. Their livers filled with pseudo-tubercles containing ova are homogenized after removal of adult worms and dried. A 1 per cent. saline extract is made up with 1:10,000 parts of ethyl mercuric thiosalicylate, as preservative and can be stored in cold, of this 0.1 ml. diluted to 1:1,000 or 1:2,000 is injected intradermally. The control is 0.1 ml. saline containing the same amount of preservative. The results are read after 15 minutes. The intradermal reaction is limited by cross-reactions in infections by other trematodes.

Okabe and Tanaka (1959) have elaborated a precipitin test in the urine which is positive. The antigen is made from the eggs, cercariæ and adult worms.

The disease in its terminal stage has to be differentiated from Banti's disease and from kala-azar. Campbell states that most cases diagnosed as Banti's disease in the Far East are in fact schistosomiasis japonica. Louchs suggested that a safe method of making a positive diagnosis is by biopsy of the liver during splenectomy, and the demonstration of the eggs, when they are not apparent in the fæces. Sigmoidoscopy, as in *S. mansoni*, is of value. The lesions are found in the region between the second rectal valve and the rectosigmoid junction, 10-15 cm. from the anus. The acute stage is characterized by œdema, congestion and yellow spots containing ova, 1-6 mm. in diameter (Plate XIV). In the chronic stage the mucosa is hypertrophic and thickened with multiple brownish depressions and looks "pockmarked." Solitary polyps are also seen. In the dysenteric form the mucosa shows irregular ulcers. Ova may be demonstrated by "scrape biopsy." Sometimes repeated examinations of the stool fail to reveal eggs. Pathognomonic lesions are found in 67 per cent. of cases. (P'an Sun and colleagues, 1957). Crypt-aspiration is of great value to demonstrate eggs (Hollands and Palmer, 1946). This method consists of a heavy-walled bent-tipped glass pipette connected with a motor-driven suction pump, developing 20 in. mercury vacuum. Suspicious lesions are scraped and then aspirated. Differential diagnosis has to be made also from Jacksonian epilepsy, cysticercosis and tumours of the brain, since deposition of *S. japonicum* eggs in the cerebral cortex may give rise to granulomata of considerable size.

Treatment.—Antimony tartrate, given in the same doses and in the same manner as for *S. hæmatobium*, appears to be efficacious in killing adult trematodes in the early stages. A total amount of 24 gr. or more is necessary. In China no difference in toxicity is noted between the potassium and sodium salts. In mass treatment the drawback is keeping the patient too long from work. Satisfactory results are now being achieved by reducing the standard 20-25 days treatment to that of one week. A cure is assessed as egg-free state after one year. Complications are hepatic coma and mental symptoms. Reduction of protein intake sometimes leads to rapid and dramatic improvement. *Miracil D* has no effect upon *S. japonicum*.

Unfortunately, in China and Japan patients usually apply for treatment only when in the advanced stages; in these the intestinal ulceration and hepatic cirrhosis are generally so pronounced that drug treatment is of little avail. There have been no reports, up to date, of the application of T.W.Sb. (Friedheim) to *S. japonicum*.

Operative treatment.—Surgical measures employed in China included cross-circulation techniques such as splenorenal or portocaval anastomosis and ligation of the hepatic artery have been carried out for the relief of portal hypertension. Cases have lived for years after operation.

Prophylaxis.—Water reported to cause the disease should be boiled, or avoided, for drinking or bathing purposes. Sportsmen, if they must frequent such regions, should wear rubber boots or waders. It must be remembered that the snail hosts are amphibious. Lime in a solution of 1 in 1,000 is the most economical reagent for the extermination of the intermediary host and kills cercariæ in thirty minutes. It is especially recommended because of its added value as a fertilizer. The prophylaxis of this form of schistosomiasis presents many difficulties, for the disease attacks domestic animals, especially pigs and dogs, as well as man. The snail vectors, moreover, live in almost inaccessible situations in channels, overhanging banks and ditches, and, being operculated, can withstand drought with impunity. It has been shown by Rose that those snails which are heavily infected do not propagate, as infection with cercariæ destroys the genital glands. The most successful molluscicides are dinitro-o-cyclo-hexylphenol and its dicyclohexyl-amine salt which destroy not only the snails but also eggs and cercariæ of *S. japonicum*.

In 10 parts per million, sodium pentachlorophenate acts best in flowing water against oncomelania. It should be sprayed on moist surfaces where colonies are living, but the former compound is better in 3-5 parts per million against all stages of aquatic snails.

Hunter (1954) found results so favourable that schistosomiasis could be eradicated from Japan in 5-7 years.

These compounds are too toxic to fish and are ineffective in cold weather.

In China the combination of spraying and ditching is already exerting a considerable effect upon the numbers of the intermediary host.

During the summer months large numbers of snails are found on land, 1½-2 metres from the water's edge. Spraying, burning and scalding are all effective killing measures. A cheaper technique of spraying with poisonous chemicals, such as calcium arsenite is restricted to ditches, canals or fields.

Burning of grass on the banks of small creeks and ditches is carried out by means of portable flame throwers carried on the shoulders and in wheelbarrows. The banks of the large canals are scorched, by similar means mounted on punts and burning carbon monoxide gas. Those snails embedded in mud which are not destroyed by burning or spraying have to be killed by other means. Some can be suffocated by filling in old ditches and by digging new ones.

These measures have been followed by the reduction of snails by 98 per cent. in some areas.

Promiscuous defæcation is controlled by storage of fæces up to a week before use in the fields which permits the ammonia generated to destroy the ova. In most villages each family has its own collecting pots which are emptied daily into tanks. This together with properly supervised washing of communal vessels prevents contamination of ditches and canals.

The satisfactory disposal of animal fæces, such as cows and water buffalos presents a major problem. Coprophagous pigs also continue to pass viable ova.

CHAPTER XLV

PARASITES OF THE LYMPHATIC SYSTEM AND CONNECTIVE TISSUES : FILARIASIS

Definition.—Morbid conditions produced by certain nematode worms, or filariæ, the adults of which, of both sexes, live in the lymphatics, connective tissues or mesentery, producing live embryos, or microfilariæ, which find their way into the blood-stream where they are capable of living for a considerable time without developing further.

The embryonic form is referred to in this manual as *microfilaria bancrofti* (Fig. 185, 1); the other filariæ of the blood are named *microfilaria loa* (or *mf. diurna*) (Fig. 185, 2), *microfilaria malayi* (Fig. 185, 3), *microfilaria volvulus* (Fig. 185, 4), *microfilaria ozzardi* (*mf. demarquayi*) (Fig. 185, 6), and *microfilaria perstans*, the embryo of *Dipetalonema perstans* (Fig. 185, 5).

The filariæ less important from a pathological standpoint are dealt with in the Appendix (pp. 999–1019).

I. FILARIASIS DUE TO WUCHERERIA BANCROFTI

Geographical distribution and prevalence.—*Wuchereria bancrofti* occurs indigenously in almost every tropical and subtropical country, from Charleston in the United States and Southern Spain in Europe to Brisbane in Australia. It is extremely common in India and South China, where in some areas nearly 60 per cent. of the inhabitants are affected. It is also found in the West Indies, South America, North Africa, Southern Sudan, West and Central and East Africa (Map XI). The form in Samoa, Fiji and other Pacific Islands, produces widespread disease, and is known as *W. bancrofti*. var. *pacifica*.

If the individuals who exhibit the microfilaria in their blood be reckoned in addition to those who exhibit the pathological effects of filarial disease, but in whose blood the microfilaria is no longer to be found, the incidence of filarial disease in some of the Pacific islands is very high—as high as 80 per cent.

Ætiology. Parental forms.—The parent filariæ (*Wuchereria bancrofti*) and the Pacific form (*W. bancrofti*. var. *pacifica*) have been found many times. They are long, hair-like, transparent nematodes, 2–3 in. in length (Figs. 186, 187). The sexes live together, often inextricably coiled about each other. Sometimes they are enclosed, coiled up several in a bunch and tightly packed, in little cyst-like dilatations of the distal lymphatics (Maitland); sometimes they lie more loosely in lymphatic varices; sometimes they inhabit the larger lymphatic trunks between the glands, the lymphatic glands themselves, and probably not infrequently, the thoracic duct.

The female worm is almost twice the length of the male, and considerably broader. The fully-mature and fecundated female filaria gives birth during

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her lifetime to an unending stream of living embryos, or microfilariae, which emerge from the vaginal orifice. That of the Pacific variety, both male and female, are smaller and there may be some minor morphological distinction. (For further details, see Appendix, p. 1006.)

Opportunities have arisen for the study of the life history of *W. bancrofti*. var.

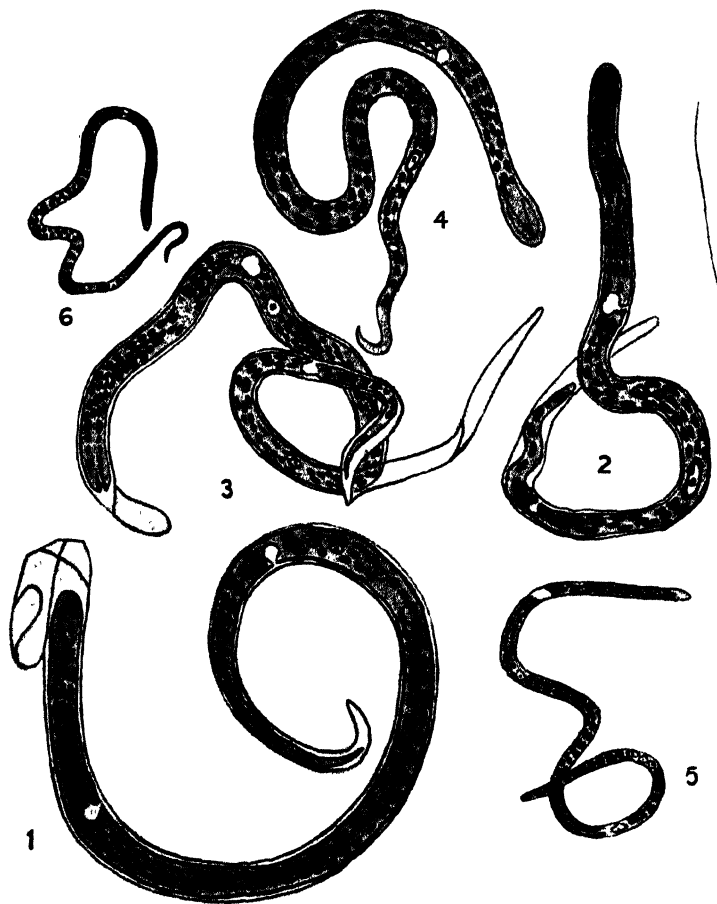


Fig. 185.—Human microfilariae ; 1, *Mf. bancrofti* ; 2, *Mf. loa* ; 3, *Mf. malayi* ; 4, *Mf. volvulus* ; 5, *Mf. perstans* ; 6, *Mf. ozzardi*. (Drawn to scale.)

pacifica in over 1,000 marines who have returned to America from Saama. After 3-6 months' residence there acute manifestations of filariasis resulted. Immature worms have been removed from fugitive swellings in the subcutaneous tissues, but very few microfilariae have been discovered in the blood. This is consistent with the view that it takes approximately three months to one year to complete development in the human body (Faust, 1944). (See also p. 1006.)

The life-spans of *W. bancrofti* and its microfilariae have not been finally determined. From the fact that the microfilariae have been found in the blood, long after the opportunity of infection has passed, it is concluded that the adults may live for twelve years or longer. The embryo filariae sometimes disappear completely from the circulation within a few hours of the death of the parent worms during an attack of lymphangitis.

As shown by Wise and the Editor, the mature worm becomes cretified after its death, and may be found in this condition in the lymphatic vessels and glands, sometimes in large numbers (Fig. 188), and it has been found by the Editor originally, that the adult filariae, whether alive or dead, cause occlusion of the lymph vessels and thereby contribute towards general lymph stasis.

According to O'Connor, microfilariae are destroyed in the substance of the lymphatic glands and are responsible to some extent for the pathological changes



Fig. 186.—*Wuchereria bancrofti* (enlarged), left, male ; right, female.
(Dr. M. Oesterlein.)



Fig. 187.—*Wuchereria bancrofti* (natural size), left, male ; right, female.

found in these structures. He showed that they are broken up in the lymph-node sinuses ; and that this is the common method of destruction of foreign substances in lymph-glands has been demonstrated by Indian-ink injection methods by Drinker, Wislieki and Field. McMullen (1937) described a case in an Indian, infected with *W. bancrofti*, in whom the microfilariae were detected, by means of the slit lamp, in the anterior chamber of the eye. No visible eye lesions were present.

The microfilariae.—When present in large numbers in the blood-stream, microfilariae may be recognized in wet film preparations ; but, when the parasites are scanty, or for the examination of a large number of persons, it is often necessary to examine a considerable quantity of blood (20 c.mm.) in thick-drop preparations, dried and then dehaemoglobinized. When seen in fresh blood the embryo filaria is a snake-like organism which, without materially changing its position, wriggles about very actively.

When dead and stained, the embryo is seen to be enclosed in a sheath (Fig. 189). On measurement, it is found to be about $280\ \mu$ by $7\ \mu$.

At the anterior extremity of the living microfilaria can be seen a minute spicule, which is shot out and as rapidly retracted, and it is thought by some that the head is sheathed by a serrated "prepuce" (Fig. 190). In a fresh blood preparation the spicule can be seen disturbing cells at some distance away.

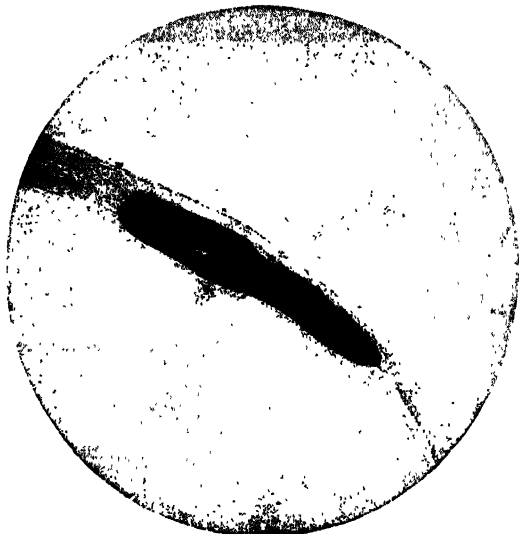


Fig. 188.—Calcified *Wuchereria bancrofti*, var. *pacifica* lying in and blocking a lymphatic vessel.

Brug and Rodenwaldt described in the Dutch East Indies the embryo of another filaria (*Brugia malayi*) which has a wide range in Malaya, Ceylon, India, Dutch East Indies, Indo-China, and South China (Fig. 185, 3). Development takes place in a number of mosquitoes of the genera *Mansonioides* and *Anopheles*. The adult stage of *B. malayi* was described by Rao and Maplestone in 1938. In the Pacific form *W. bancrofti* development takes place in *Aedes scutellaris pseudo-scutellaris* and *A. s. polynesiensis*.

Filarial periodicity.—A singular feature in the life of the microfilaria is what is known as "filarial periodicity."

If, under normal conditions of health and habit, the blood be examined during the day, the microfilaria is rarely seen, or, if it be seen, only one or two specimens at most are encountered in a slide. But towards evening they begin to appear in gradually increasing numbers. The swarm goes on increasing until about midnight, at which time it is no unusual thing to find as many as three hundred, or even six hundred, in every drop of blood; so that it has been calculated that as many as forty or fifty millions are simultaneously circulating in the blood-vessels. After midnight the numbers begin gradually to decrease; by eight or nine o'clock in the



Fig. 189.—*Microfilaria Bancrofti*, var *pacifica* in hydrocele fluid. The embryo on the right has escaped from its sheath.

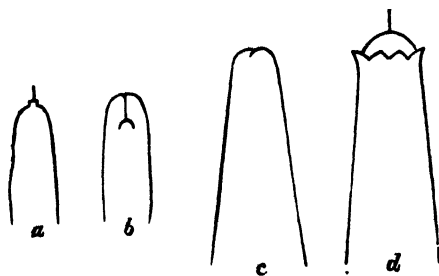


Fig. 190.—Structure of head end of *Microfilaria perstans* (*a*, *b*) and of *Microfilaria bancrofti* (*c*, *d*).

morning the microfilariae have disappeared from the peripheral blood for the day. This nocturnal periodicity, under normal conditions, is maintained with the utmost regularity for as many as twelve years, as in the

cases recorded by the Editor. Should, however, as Mackenzie has shown, a filarial subject be made to sleep during the day and remain awake at night, after a period of three to four days the periodicity is reversed; that is to say, the parasites come into the blood during the day and disappear from it during the night. It cannot be the sleeping state, as some have conjectured, that brings about this periodicity; for the ingress of the microfilariae into the peripheral blood commences three or four hours before the usual time for sleep, and the egress several hours before sleep is concluded, and this egress is not complete until several hours after the usual time of waking. This night swarming of the embryos of *W. bancrofti* in the peripheral circulation has been regarded as an adaptation correlated

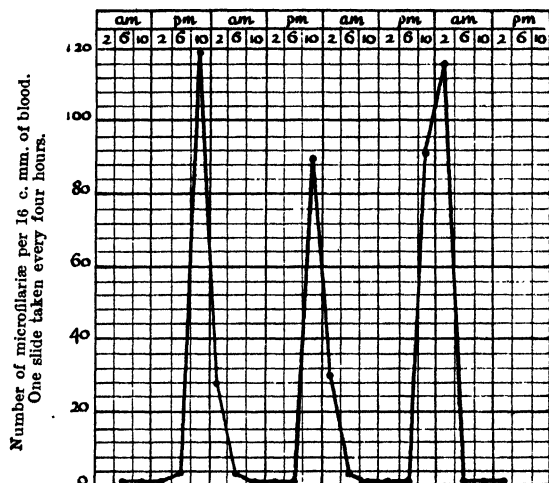


Chart 28.—Filariasis (*W. bancrofti*, *Microfilaria nocturna*), showing nocturnal periodicity (orig).

to the life-habits of its liberating agent, the mosquito, *Culex fatigans*, its common intermediary host. (Chart 28.) (See also p. 1003.)

It has been demonstrated that the periodicity of the filaria of the American crow is to some extent affected by light and darkness. Hawking has shown that acid intravenous infusions cause an increase of microfilariae in the capillary blood, whilst alkaline ones may cause the reverse.

Non-periodic microfilaria bancrofti.—Formerly it was thought that nocturnal periodicity was uniformly observed by microfilariae of *W. bancrofti* at all times and in every country. In 1896 Thorpe remarked that in Tonga and Fiji the microfilaria could be found often in great abundance in the blood during the day as well as in the night, but, strange to say, it has since been ascertained that the microfilariae of neighbouring islands in the Pacific—namely, the Solomons, New Guinea and the Bismarck Archipelago—are nocturnal periodic.

The Editor demonstrated that the microfilariae of Indian immigrants who have acquired their filarial infections in India retain their periodic habits during at least three years of residence in Fiji, but that if an Indian or a Solomon Islander acquires the infection in Fiji the microfilariae are non-periodic in habit.

As an explanation of this striking anomaly, the non-periodic microfilaria is the progeny of a parent worm specifically distinct from *W. bancrofti*, for which the variety *pacifica* is now suggested, which produces certain pathological peculiarities such as elephantiasis of the arms. Fülleborn and the Editor, after minute study



Fig. 191.—Section of lung showing microfilariæ in alveolar capillaries. (Microphotograph : Dr. H. Spitta.)

and comparison of the microfilariæ from these countries, found that they are morphologically identical.

The habitat of microfilariæ.—In lung sections (Fig. 191) the microfilariæ lie outstretched or variously coiled in the vessels, large and small. In the heart-muscle they are found in the capillaries between the fibres; in the kidneys they seem especially to affect the Malpighian tufts; a very few are also found in the capillaries of the brain; vast numbers are present in smears from the inner surface of the carotid arteries. Preparations afford no explanation of how the microfilariæ contrive to maintain their position in the blood-current, or of the forces determining their peculiar distribution.

The mosquito the intermediary host of W. bancrofti.—If the females of certain species of mosquito (*Culex fatigans*) which have fed on the blood of a filaria-infected person are examined immediately after feeding, the blood in the stomach will be found to harbour large numbers of living microfilariæ, while a few hours

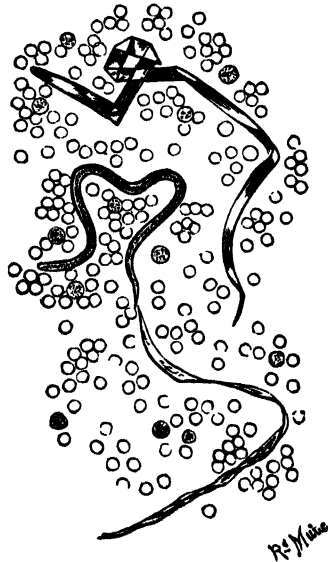


Fig. 192.—Microfilaria casting their sheath.

afterwards many of them will be seen actively endeavouring to escape from their sheaths. Change in the viscosity of the blood seems to prompt them to escape. After a time the majority succeed in effecting a breach and in wriggling themselves free from the sheaths which had hitherto enclosed them (Fig. 192). This process can be induced by chilling wet blood preparations on ice and then allowing them to thaw at room-temperature. For details of development on the mosquito, see Appendix, p. 1003. Eventually the filaria in its progress, enters the proboscis, where, as pointed out by Grassi, its exact position is the interior of the proboscis-sheath (labium) (Fig. 193).



Fig. 193.—*W. bancrofti* in head and proboscis of mosquito. (G. C. Low.)

a, a, a, Filariae; b, labium; c, labrum; d, base of hypopharynx; e, duct of veneno-salivary gland; f, f', cephalic ganglia; g, g', eye; h, oesophagus; i, pharyngeal muscle.

The parasites remain in the proboscis, awaiting an opportunity to enter a warm-blooded vertebrate host when the mosquito next feeds. They appear to do so by penetrating the thin membrane that unites the labella to the tip of the proboscis-sheath, and so pass on to the surface of the skin, which they penetrate in the neighbourhood of the puncture made by the mosquito. Sometimes the larval filaria dies and becomes chitinized (Fig. 194).

The filaria is introduced into its human host through the agency of a mosquito-bite. Once introduced into the human body, the filaria finds its way into the lymphatics and glands, where it attains sexual maturity in five to eighteen months

(Wartman, 1957), though in American marines in Samoa adult worms were recovered within three months of first exposure. In due course new generations of embryo filariae (microfilariae) are poured into the lymph. These, passing through the gland—if such should intervene—by way of the



Fig. 194.—Chitinized larval filaria in thorax of mosquito.

thoracic duct and left subclavian vein, or by the lymphatics of the upper part of the body, finally enter the circulation.

Epidemiology and endemiology.—In most countries in which filariasis is common it appears to be the rule that the incidence of infection is greatest in the male, though in British Guiana Daniels and Conyers found twice as many females infected as males. This exception to the general rule probably finds an explanation in the habits of the natives who are infected at night in their houses, especially in Georgetown. The Editor's statistics from Fiji showed that of 1,820 people of Fijian blood, 80.4 per cent. of males and 28.9



Fig. 195.—Section of a fibrosed lymphatic gland.

A, Portions of a calcified *W. pacifica*; B, partially occluded lymphatic vessel.
(Philip Manson-Bahr)

per cent. of females were filariated. The incidence is greatest in both sexes after the twentieth year; comparatively more females than males are infected below the age of ten. This, however, is not the invariable rule in the Pacific. In Samoa, Jackowski and Otto, found in some Samoan villages the highest incidence was in women, and this has been confirmed by Iyengar in the Cook Islands (1957). This proportion is probably due to the hazards of exposure to infection in the course of occupation in coconut plantations. The youngest infected patient—a child of 14 months—was recorded by Anderson in British Guiana. As a general rule the microfilaria rate shows a gradual, but continuous rise from 2.5 in the 1-4 age group to 24.5 in the last (50 years or over), after which the curve flattens out and the subsequent rise is not proportional to increase in age. Gross signs of filarial disease become apparent in age

group 20-29 years. As in the Pacific so in the Philippines, where Rozeboom and Calvera have suggested an association between the incidence of *W. bancrofti* infection and the cultivation of Manila hemp, and where also the rate of infection is higher in adult males than in females because they are more exposed to the bites of the vector mosquitoes. The rate of filariation*varies considerably in different islands of the Pacific, even in different districts of the same island, and is in direct proportion to the incidence of elephantiasis and other filarial diseases. In 1912 in Ceylon the Editor found that, whereas 26 per cent. of the adults of some villages were infected, in neighbouring hamlets the inhabitants were quite free

from these parasites and their associated diseases.

Pathology.—*The filaria not generally pathogenic.*—In most cases of filarial infection the parasite exercises no manifest injurious influence whatever. In a certain proportion, however, there can be no doubt that it does exert a prejudicial effect, and this mainly by obstructing lymphatics. Healthy, fully-formed microfilariae—that is to say, the embryonic filariae in the blood—are, so far as we can tell, harmless.

Filarial disease originating in injury of lymphatic systems.—Roughly speaking, the filaria causes two types of disease: one characterized by varicosity of lymphatics, the other by more or less solid cedema. The exact way in which the parasite operates has not been definitely and absolutely ascertained for all types of filarial disease. Apparently, in some instances a single worm, or a bunch of worms, may plug the thoracic duct, and act as

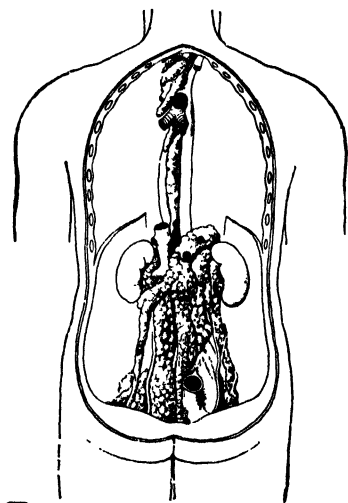


Fig. 196.—Dissection of the lymphatics in a case of chyluria, showing the dilated right and left renal lymphatics and the thoracic duct. (Mackenzie, "Trans. Path. Soc. Lond.")

an embolus or originate a thrombus; or, the worm may give rise to inflammatory thickening of the walls of this vessel, and so lead to obstruction from the consequent stenosis or thrombosis. In other instances the minor lymphatic trunks and the glands may be similarly occluded. (Fig. 195.)

The afferent lymphatic glands situated at some considerable distance from the actual seat of the filaria worms (for instance, the lumbar glands) undergo considerable changes, such as fibrosis, focal necrosis, giant-cell formation, macrophage proliferation and aggregation of small epithelioid foci, changes which are also seen in the lymphatic vessels and periglandular connective tissues. The resemblance to tuberculoid focal granulomata is close. These changes may be due partly to the destruction of microfilariae within the gland substance, or to toxins excreted by the adult parasites. Some microfilariae undergo calcification, and thereby cause endothelial proliferative outgrowths in the lymphatic channels.

There now appears to be little doubt that the pathological effects produced by *W. bancrofti*. var. *pacifica* are more severe and extensive than those due to *W. bancrofti*.

Early manifestations have been well described by American observers in the Pacific area in marines and soldiers. They are allergic in nature and consist of fugitive, tender and painful swellings like *erythema multiforme*, especially on the arms. There is lymphadenitis also of the neck, axilla and groin. Biopsy studies show changes similar to those produced by injections of *Dirofilaria immitis* antigens. When the parent worms are bunched together lymphangitis appears with the liberation of microfilariae into the tissues. Associated with these phenomena are generalized pains, testicular pain and funiculitis. Moderate emaciation results (Leede and Josey, 1945). Hypersensitivity is probably the explanation of most of these phenomena and the intradermal test is usually positive. Romiti, from his extensive experience in British Guiana, considers that the earliest, most reliable and usually the *only* physical sign is a varico-lymphocele of the spermatic cord. In filarial patients the dilatation of the vessels of the group is distributed along the spermatic artery and the pampiniform plexus.

Classification of the pathological manifestations is difficult. Clinton Manson-Bahr has suggested division into three stages: primary or allergic; secondary or carrier; and tertiary or obstructive.

The *primary or allergic stage* may be simulated by injection of *Dirofilaria immitis* antigen and consists of eosinophilic infiltration of glands and subcutaneous tissue around the immature filarial worms. In this manner lymphangitis, funiculitis and orchitis are brought about.

The *secondary or carrier stage* may last from two to seven years after infection—that is till the filarial worms have matured and the microfilariae have entered the circulation as was shown by Michael and Neumann in American soldiers infected in the Pacific in the recent war.

The *tertiary or obstructive stage* is caused by destruction of the lymphatic filter of the lymph glands with consequent blocking and dilatation of the lymphatics. As a result of the lymphatic obstruction there occurs a transudation into the tissues of lymph rich in protein which causes a cellular proliferation of the connective tissues with the production of elephantiasis.

Pathology of lymphatic varix.—In consequence of the rich anastomosis between contiguous lymphatic areas, a compensatory lymphatic circulation is sooner or later established. But before this can be thoroughly effected a rise of lymph-pressure and a dilatation of the lymphatics in the implicated area must take place. This leads to lymphatic varix of different kinds, degrees and situations. When the seat of filarial obstruction is the thoracic duct, the chyle poured into that vessel can reach the circulation solely by a retrograde movement; this fluid may therefore be forced to traverse in a retrograde way the abdominal and pelvic lymphatics, the lymphatics of the groin, scrotum, and abdominal wall. As a consequence, these vessels, together with the thoracic duct up to the seat of obstruction, become enormously dilated. In dissection of such cases (Fig. 196) the thoracic duct has been found distended to the size of a finger, the abdominal and pelvic lymphatics forming an enormous varix, perhaps a foot in diameter and some inches in thickness, concealing kidneys, bladder, and spermatic cords. In such cases, when one of the vessels of the varix is pricked or ruptures, the contents are found to be white or pinkish. They are not limpid like ordinary lymph. They are chyle, therefore—chyle on its way to enter the circulation by a retrograde compensatory track. When the varix involves the integuments of the scrotum, the result is “lymph scrotum” (Fig. 201); when most prominent in the groin, then a condition of glands is

produced which Manson termed "varicose groin-glands"; when the lymphatics of the bladder or kidneys are affected and rupture from over-distension, then chyluria is the result; when those of the tunica vaginalis rupture, then there is chylous dropsy of that sac—"chylocele"; but when rupture is into the peritoneum—chylous ascites. Occasionally, varicose lymphatic glands resembling those in the groin are found in the axilla. Occasionally, also, limited portions of the lymphatic trunks of the limbs are similarly and temporarily, or more permanently, distended. This, doubtless, is the pathology of all those forms of filarial disease characterized by visible varicosity of lymphatics, with or without lymphorrhagia.

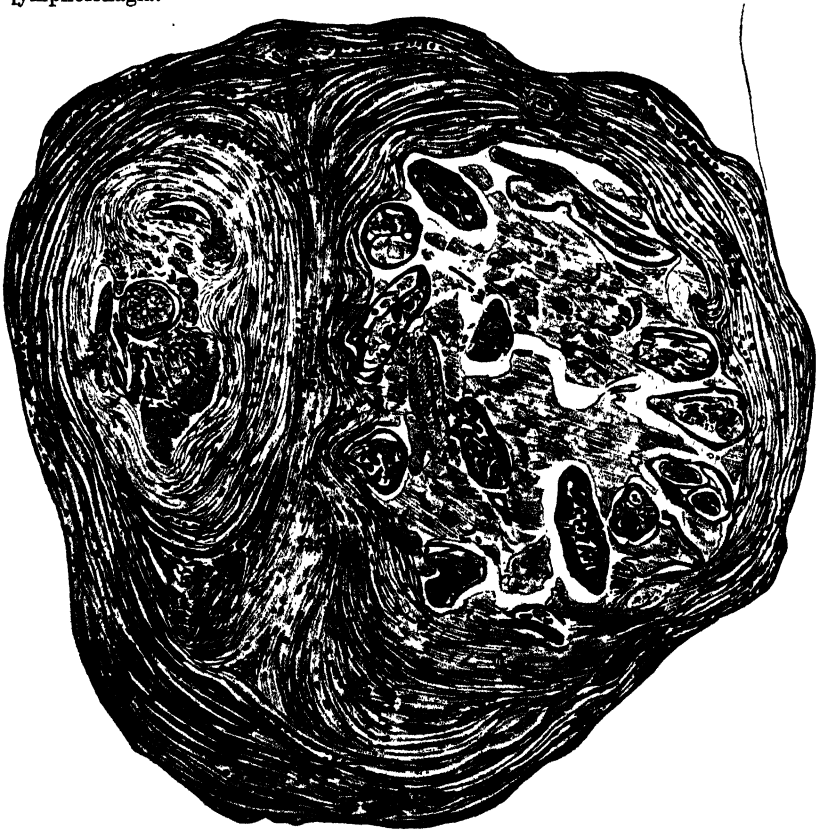


Fig. 197.—Section of a thickened brachial lymphatic containing portions of dead filariæ undergoing disintegration and blocking the lumen of the vessel. Note the large amount of fibrosis. (Philip Manson-Bahr).

Pathology of elephantiasis.—*Reasons for regarding elephantiasis as a filarial disease.*—(1) The geographical distribution of *W. bancrofti* and that of elephantiasis correspond; where elephantiasis abounds, there the filaria abounds, and *vice versa*. (2) Filarial lymphatic varix and elephantiasis occur in the same districts, and frequently in the same individual. (3) Lymph scrotum, unquestionably a filarial disease, often terminates in elephantiasis of the scrotum,

(4) Elephantiasis of the leg sometimes supervenes on the surgical removal of a lymph scrotum. (5) Elephantiasis and lymphatic varix are essentially diseases of the lymphatics. (6) Filarial lymphatic varix and true elephantiasis are both accompanied by the same type of recurring lymphangitis. (7) As filarial lymphatic varix is practically proved to be caused by the filaria, the inference appears to be warranted that, with rare exceptions, the elephantiasis of warm climates—the disease with which lymphatic varix is so often associated and has so many affinities—is attributable to the same cause (Fig. 197).

In filariated subjects a process of proliferation of the endothelium of the lymphatic vessels takes place—a species of lymphangitis, first described by the Editor and later confirmed by O'Connor; it is due to the action of the microfilariae which become imprisoned in the endothelial lining of the vessel (Fig. 198), and is probably fostered by the stimulating action of the lymph upon cellular proliferation.

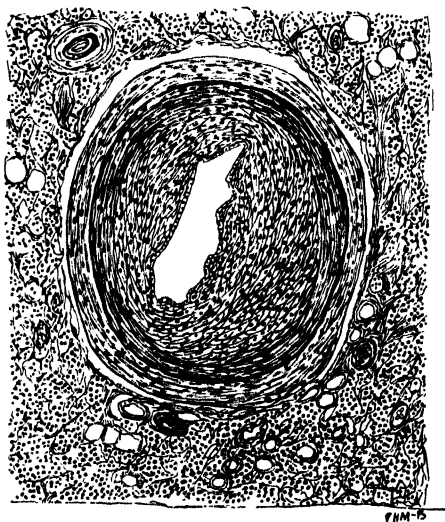


Fig. 198.—Occlusion of lymphatic vessels by proliferation of the endothelium in filariasis (*obliterative endolymphangitis*).

Diagnosis.—Diagnosis is made by demonstration of the microfilariae in the night-blood; usually 20 c.mm. are necessary for the purpose, the thick-drop method being employed (*see p. 1091*). But for reasons already stated the embryos may not always be present. There is usually an appreciable eosinophilia which is most marked in the allergic stage.

Knott's method of concentrating the microfilariae is most useful in scanty infections and for conducting filarial mass surveys. This consists of abstracting 1 ml. of venous blood from the antecubital vein. This is diluted in 2 per cent. formalin in distilled water 9 ml. and then centrifuged. The microfilariae are found massed in the precipitate.

Serological and intradermal tests in filariasis.—These tests were introduced by Fairley, Taliaferro and Hoffman. The antigen is prepared from *Dirofilaria immitis* of the dog, *Dracunculus medinensis* or *Setaria equini* or *S. cervi*, diluted 1 : 4,000–1 : 8,000, which is washed and dried, it being estimated that 1 gm. is extracted from 250–300 worms. An alcoholic is more potent

than a saline extract of the antigen. A positive complement-fixation is given with most cases of *W. bancrofti* filariasis; but it is a group reaction, and appears to be more reliable in *L. loa* than in *W. bancrofti*, but is also positive in *Onchocerca volvulus*. Lloyd and Chandra obtained the most reliable results with an antigen derived from the acetone-insoluble lipoids of *D. immitis* by the process used by Bordet for syphilitic antigen. Extracts of the filaria of the cotton rat—*Litomosoides carinii*—have been prepared and give positive reactions in 77 per cent. (Goodman *et al*, 1945).

The intradermal test is based on the same immunological principles. Fairley uses 0.25 ml. of a 0.1 per cent. extract as antigen. An immediate (30 min.) and delayed reaction are obtained; the latter may become indirect after a period of forty-eight hours. A wheal over 2 cm. in diameter is regarded as positive. Antigen controls should be instituted by similarly diluted horse protein. Opinions vary about the reliability of this test. In the ' it is vitiated by the concurrence of intestinal nematode infections. (1947) concludes that, though in some degree, diagnostic, this test cannot be wholly depended upon. On the other hand, Wharton (1947) finds that cross reactions with intestinal helminths are not infrequent. The immediate reaction is erythema from 1-4 cm. in all degrees to wheals with pseudopodia. It takes 15 min. to 1 hour to develop: the delayed reaction takes place after 24 hours with oedema.

Technique. *Preparation of antigen for complement-fixation test.*—Technique similar to that described for schistosome cercarial antigen is employed, 0.5 gm. of the dried powdered *Dirofilaria immitis* being extracted with 50 ml. of 98 per cent. alcohol for 24 hours at 37° C. Well shaken by hand several times during this period, it is filtered through Whatman No. 1 and a Buchner filter. The filtrate is subsequently concentrated by bubbling air through the solution kept at a temperature of 40° C. by immersion in a water-bath till turbid; this turbidity is then removed by adding 8 ml. of fresh alcohol, making the total volume 25 ml. The resulting extract is then stored in the ice-chest in amber-coloured ampoules of 1 ml. capacity. The technique of putting up the test is similar to the standard advocated for serological diagnosis of schistosomiasis.

Preparation of antigen for intradermal test.—Fifty ml. of a 1 per cent. saline extract of dried powdered antigen is incubated for two hours at 37° C., being well shaken by hand from time to time. Subsequently it is passed through a Whatman No. 1 filter paper, then through a Buchner filter, and is then sterilized by passage through a sterile Seitz asbestos filter. The filtrate is put up in dark glass ampoules and stored on ice.

Pandit's reaction is an adhesion phenomenon and is also known as the Rieckenberg reaction. When blood containing microfilaria is mixed with serum from a case of filarial elephantiasis and kept at room temperature for an hour or longer, the embryos become sluggish and surrounded by adherent leucocytes.¹ (Raghavan). Phenomena of agglutination and thigmotaxis of microfilariae have been observed *in vitro* in heparinated venous blood by Yoeli (1957). Distinct patterns of "Medusa head" and sunflower formations of the agglutinated masses of microfilariae were noted. The strict dependence of the agglutination phenomenon on the amount of heparin in the blood was clearly established and a partial release of microfilariae into the peripheral blood, during the day, as the result of intravenous heparin injections, was achieved.

Filarial elephantiasis.—The anatomical situation of elephantiasis depends upon the distribution of the afferent lymphatic vessels. It must not be thought, however, that lymphatic elephantiasis is *solely* the product

¹ The "Thorn" test is applicable to filariasis—*i.e.*, if the eosinophilia in the blood remains at the same figure after injection of 25 mgm. of cortisone or A.C.T.H.

of filarial infection. The following classification of elephantiasis has been suggested:

- (a) Congenital or familial elephantiasis (Milroy's or Meige's disease) ; stenosis of main lymphatic trunks.
- (b) Parasitic elephantiasis: *Wuchereria bancrofti*, *W. bancrofti* var. *pacifica* *Brugia malayi*, or *Onchocerca volvulus*.
- (c) Septic elephantiasis (*Elephantiasis nostras*—lymphatic infection by streptococci).

Elephantiasis is also produced by *Brugia malayi*. The difference between the two forms of lymphatic obstruction seems to lie in the predilection of this parasite for the legs rather than for the genitalia and scrotum as in *Wuchereria bancrofti* infestation. Elephantiasis of the scrotum also occurs in *Onchocerca volvulus* infections.

In most cases the real origin of the obstruction lies in the fibrotic changes induced by the parasite in the lymphatic vessels and glands. Lymph stasis in lymphatic vessels alone does not produce elephantiasis which has been proved by ligature of the lymphatic trunk, resulting in œdema, but not in true elephantoid hypertrophy.

There is some reason for believing that damage to the lymphatic vessels makes them susceptible to streptococcal and staphylococcal infections.

O'Connor demonstrated that in filarial lymphangitis focal spots can be distinguished from which the inflammatory process commences, indicating the sites of dead filariæ. This observer, with Golden and Auchincloss, found that in filariated subjects, especially in elephantiasis, calcified filariæ may be demonstrated by X-rays. The shadows range from 1 mm. in width to 2-3 mm. in length. Fifteen shadows, or groups of shadows were detected in one elephantoid leg.

In some such manner can be explained the production of elephantiasis by the filaria, and the absence from the blood of the embryos glands. Probably the parent worm, or worms, die at an early stage of the disease, killed by subsequent lymphangitis, or some other undertermined cause.

SYMPTOMS, DIAGNOSIS, AND TREATMENT OF FILARIAL DISEASES

Enumeration of filarial diseases.—The diseases known to be produced by or associated with *W. bancrofti* are—abscess ; lymphangitis ; arthritis ; synovitis ; abscess of hip-joint ; varicose groin glands ; varicose axillary glands ; lymph scrotum ; cutaneous and deep lymphatic varix ; orchitis ; funiculitis ; hydrocele ; chyluria ; elephantiasis of the leg, scrotum, vulva, arm, mamma, and other parts ; chylous dropsy of the tunica vaginalis ; chylous ascites ; chylous diarrhœa, and probably other forms of disease depending on obstruction or varicosity of the lymphatics, or on the death or injury of the parent filariæ in a lymphatic abscess—including fatal peritonitis and secondary infections by pyogenic micro-organisms (filarial abdomen). Cilento has drawn attention to the frequency of adenitis of the popliteal space in filaria-infected children in Queensland.

Abscess.—Occasionally, as already mentioned, whether in consequence of blows or other injuries, of lymphangitis, or of unknown causes, the

parent filariæ die. Generally the dead body is absorbed, just as a piece of aseptic catgut would be, or becomes cretified.¹ Sometimes the defunct worm acts as an irritant and causes abscess, in the contents of which fragments of the filaria may be found. Such abscesses, occurring in the limbs or scrotum, will discharge in due course or may be opened; if properly treated surgically, they may lead to no further trouble. Should they form in the thorax or abdomen, serious consequences and even death may ensue.

Lymphangitis and elephantoid fever.—Lymphangitis is common in all forms of filarial disease, particularly in elephantiasis, varicose glands, and lymph scrotum. It is now generally conceded that it is allergic in origin (Thook, 1956). In the limbs it is usually retrograde; the characteristic painful cord-like swelling of the lymphatic trunks and associated glands, and the red congested streak in the superjacent skin, are usually apparent at the commencement of the attack. The attack may continue for several days, and be accompanied by severe headache, anorexia, often vomiting, and sometimes delirium. After a time tension of the inflamed integuments may relieve itself by lymphous discharge from the surface. Usually, the attack ends in profuse general diaphoresis. Lymphangitis may be confined to groin glands, testis, spermatic cord (endemic funiculitis) or abdominal lymphatics. When it affects an extensive abdominal varix, symptoms of peritonitis rapidly develop, and may prove fatal. The evidence at present available is that lymphangitis represents an allergic response to the presence of adult worms.

In the Pacific islands a form of filarial fever is commonly met in heavily-infected districts, unassociated with lymphangitis; this probably represents inflammation of the deep-seated lumbar lymphatics or glands. It has been pointed out by Winkel and Fros (1952) that hetrazan treatment often provokes one of these attacks.

Diagnosis.—This fever, usually termed "elephantoid fever," occurs at varying intervals of weeks and months, or years, in nearly all forms of elephantoid disease. Its tendency to recur, the severe rigor, and the terminal diaphoresis, caused it to be mistaken for malaria. In Barbados, where there was until recently no malaria, it was habitually called "ague." In Samoa it is known as "mumu fever"; in Fiji as "wanganga." In India, Rao and Sukhatne believed that there exists a periodicity in the incidence of lymphangitis, which is greatest during the monsoon period, July to September, when humidity is high.

Treatment.—Treatment should consist in removing any cause of irritation, in rest, elevation of the affected part, cooling lotions, mild aperients, opium or morphia to relieve pain, and, if tension is great, pricking or scarifying the swollen area under suitable aseptic conditions. Subsequently the parts, if their position permits, should be elevated and firmly bandaged.

Sulphonamides have been used. Sulphathiazole and sulphadiazine and

¹ Wise and Minett found filariæ, living or cretified, in the following situations: pelvis of kidney (31 times), epididymis (18 times), retroperitoneum (12 times), ilio-psoas muscle (4 times), Gilson's capsule (twice), inguinal glands (26 times), lymphatic vessels (8 times). Similar observations were made by the Editor in Fiji.

other sulphonamides have been given with apparent success, especially when combined with penicillin. *Anthisan*, and other anti-histamine drugs are indicated.

Varicose groin-glands (Fig. 199).—Varicose groin-glands are frequently associated with lymph scrotum, with chylous dropsy of the tunica vaginalis, or with chyluria. Occasionally all four conditions may co-exist in the same individual.

As a rule, the patient is not aware of the existence of varicose glands until they have attained considerable dimensions. Then, a sense of tension, or an attack of lymphangitis, calls attention to the state of the groins, where certain soft swellings are discovered. These swellings may be of insignificant dimensions or they may attain the size of a fist. They may involve both, or only one groin; they may affect the inguinal glands, or the femoral glands alone, or (more usually) both sets. Remnants of *microfilaria* can be demonstrated within giant cells in these enlarged glands.

Diagnosis.—It is important to be able to diagnose these tumours from hernia, for which they are often mistaken. This can be done by observing that they are not tympanitic on percussion; that, though pressure causes them to diminish, they do so slowly; that there is no sudden dispersion on taxis, accompanied by gurgling, as in hernia; that they convey a relatively slight or no impulse on coughing; that they slowly subside when the patient lies down, and slowly return, even if pressure be applied over the saphenous or inguinal openings, once the erect posture is resumed. The diagnosis is further strengthened by the co-existence of lymph scrotum, chyluria, or chylous hydrocele, or the presence of *microfilaria* in the blood.

Treatment.—Unless they give rise to an incapacitating amount of discomfort, and are the seat of frequent attacks of lymphangitis, varicose groin-glands are best left alone. Excision is not always satisfactory, as it may be followed by lymphorrhagia at the seat of the wound, by excessive dilatation of some other part of the implicated lymphatic area, by chyluria, or by elephantiasis of one or both legs.

Similar varicose dilatation of the axillary glands is sometimes, though much more rarely, seen.

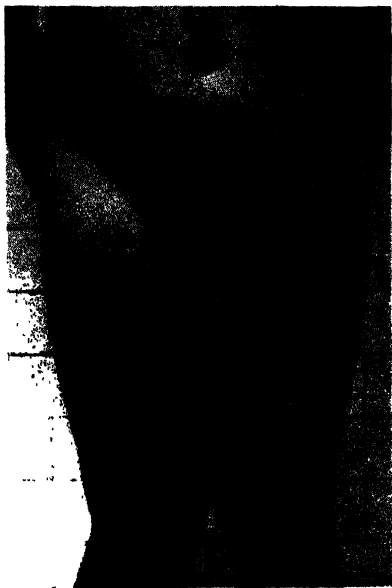


Fig. 199.—Bilateral varicose groin glands with lymph stasis and slight elephantiasis of right leg. (Dr. F. W. O'Connor, Puerto Rico.)

Thickened lymphatic trunks.—After the initial swelling and inflammation of lymphangitis have subsided, a line of induration remains. On excising this thickened tissue and carefully dissecting it, minute cyst-like dilatations of the lymphatic involved were found by Maitland, Daniels, and the Editor, and in these cysts adult filariæ, sometimes dead.



Fig. 200.—Pacific filariasis. Hydrocele and varicose groin gland.
(*P. Manson-Bahr.*)

These glands, containing adult ♂ and ♀ filariæ, were removed at operation. No microfilaria were found in the blood. There were also masses of enlarged glands in the right groin.

Filarial glandular enlargement.—In the Pacific islands great enlargement of the lymphatic glands with fibrotic changes is by far the most frequent symptom of filarial disease. The epitrochlear gland, for instance, is often affected—in Fiji in 22 per cent. of the population.

The groin-glands are often very much enlarged, sometimes to 2 or 3 in. in diameter, and may form permanent tumours in the groin. On section they resemble an unripe pear, the central portion being fibrotic, the peripheral glandular. The deep-seated glands—iliac, lumbar, mesenteric, and mediastinal—may also be enlarged (Fig. 200). Behm and Hayman (1946) have described the microscopical pathology. The predominating

cell is known as the "littoral cell" in the lymphatics and sinuses. There is also precipitation of acidophilic material about the filaria worm with necrosis, exudation of eosinophils, plasma cells, lymphocytes, proliferation of macrophages and reticular fibres. Microfilariae, when present, are also surrounded by an eosinophilic precipitate.

Treatment.—Usually it is inadvisable to remove these glands, seeing that, as with varicose groin-glands, incurable lymphocele may ensue.

Lymph scrotum (Fig. 201).—In this the scrotum is more or less enlarged. Though usually silky to the touch, on inspection the skin presents a few or a large number of smaller or larger lymphatic varices which, when pricked, or when they rupture spontaneously, discharge large quantities of milky or sanguineous-looking or straw-coloured, rapidly-coagulating lymph or chyle. In some cases 8 or 10 oz. of this substance will escape from a puncture in the course of an hour or so; it may go on running for many hours on end, soiling the clothes and exhausting the patient. Usually, microfilariae can be discovered in the lymph so obtained, as well as in the blood. In a large proportion of cases of lymph scrotum the inguinal and femoral glands, either on one or on both sides, are varicose.

Treatment.—Unless inflammation is frequent, or there is frequent and debilitating lymphorrhagia, or unless the disease tends to pass into true elephantiasis, lymph scrotum—kept scrupulously clean, powdered with boric acid, suspended, and protected—had better be left alone. Should it, however, be deemed expedient to remove the diseased tissues, this can be easily done. The scrotum should be well dragged down by an assistant while the testes are pushed up out of the way of injury. A finger knife is then passed through the scrotum, and in sound tissues, just clear of the testes, the mass is excised by cutting backwards and forwards. No diseased tissues and hardly any flap should be left. Sufficient covering for the testes can be obtained by dragging on and, if necessary, dissecting up the skin of the thighs, which readily yields and affords ample covering. It is a very common, but a great mistake, to remove too little. As a rule, the wound, if carefully stitched and dressed antiseptically, heals rapidly.



Fig. 201.—Lymph scrotum and varicose groin-glands.
(Photo: Dr. Rennie.)

Chyluria.—When a varix ruptures in the wall of the bladder, or elsewhere in the urinary tract, in the thoracic duct or in the lymphatics of the urinary system, there is an escape of the contents of the lymphatics into the urine. Chyluria is the result. If, as often happens, the urine contains blood, the condition is known as hæmatochyluria.

A curious fact about this form of filarial disease is that in the Pacific islands it is very rare, though quite common in India, China, and North Africa. It frequently appears without warning; usually, however, pain in the back and aching sensations about the pelvis and groins—probably caused by great distension of the pre-existing lymphatic varix—precede it. Retention of urine, from the presence of chylous or lymphous coagula, is sometimes the first indication of serious trouble. Whether preceded by aching, or by retention, or by other symptoms, the patient becomes suddenly aware that he is passing milky urine. Sometimes, instead of being white, the urine is pinkish, or even red; sometimes, white in the morning, it is reddish in the evening, or *vice versa*. Sometimes, while chylous at one part of the day, it is perfectly limpid at another. Chyluria is very likely to occur, either for the first time, or as a relapse, in pregnancy or after childbirth. The sanguineous appearance so frequently seen in chylous urine and in other forms of filarial lymphorrhagia possibly depends in some instances on the formation of blood-corpuscles in lymph long retained in the varicose vessels, as a result of the normal evolution of the formed elements in that fluid. In other instances it is probably caused by rupture of small blood-vessels into the dilated lymphatics; in these cases the microfilariae appear in the urine passed during the night-time only.

Physical characters of chylous urine.—If chylous urine be passed into a urine-glass and allowed to stand, within a very short time, as a rule, the whole of the urine becomes coagulated. Gradually, the coagulum contracts until, at the end of some hours, a small, more or less globular clot, usually bright red or pinkish, is floating about in a milky fluid, the appearance of which is entirely due to suspended fat particles. Later, the fluid separates into three layers. On the top there is a cream-like pellicle; at the bottom, a scanty reddish sediment, sometimes including minute red clots; in the centre the mass of the urine forms a thick, intermediate stratum, milky white or reddish white, in which floats the contracted coagulum. If a little of the sediment be taken up with a pipette and examined with the microscope, it is found to contain red blood-corpuscles, lymphocytes, granular fatty matter, epithelium and urinary salts, and mixed with these in a large proportion of cases, though not in all, microfilariae. The middle layer contains much granular fatty matter; while the upper, cream-like layer consists of the same fatty material in greater abundance, the granules tending to aggregate into larger oil globules. If a little of the coagulum be teased out, pressed between two slides, and examined with the microscope, microfilariae, more or less active, may be found entangled in the meshes of the fibrin. According to Yorke and Blacklock, the number of microfilariae in chylous urine varies greatly within the twenty-four hours in quite an irregular manner. If ether or xylol be shaken up with the milky urine, the fat particles are dissolved out and the urine becomes clear; the fat may be recovered by decanting and evaporating the ether, which floats on the urine. Boiling the urine throws down a considerable precipitate of albumin. When the urine contains only lymph, fatty elements are absent, or are present in but very small amount. According to Young, a twenty-four-hour sample of chylous urine contains 1·8–2·6 per cent.

of fat. The amount of this substance excreted is generally, though perhaps not invariably, dependent on the amount ingested.

Gottlieb and Auld (1959), in a recent analysis, found that most of the fat is in the form of neutral triglycerides, with small quantities of cholesterol, minimal amount of phospholipid, and some free fatty acid. These proportions are of the same order as in chyle. It is possible to calculate approximately the extent of the chylous leak. On a diet containing 73 grm. of fat daily, the urinary fat was about 10 grm. in twenty-four hours, showing that about 15 per cent. of the lymphatic drainage from the gut was being lost through the fistula.

Lymphuria.—It would be more correct to describe a certain proportion of filarial cases passing cloudy urine as "filarial lymphuria," as Low and Wise suggested. In these cases the abnormal element is lymph, and there is no trace of fat. Albumin is found in considerable quantity, and blood may be present as well. The chief cellular constituent is the lymphocyte. Low, who was able to investigate one of these cases shortly after death, found the lymphatic obstruction located in the kidney lymphatics, caused by calcified filariæ.

Treatment.—The treatment of chyluria should be conducted on the same lines as that of inaccessible varix elsewhere; that is to say, by resting and elevating the affected part, and thereby diminishing as far as possible the hydrostatic pressure in the distended vessels.

The best results are obtained by putting the patient to bed on an inclined plane with feet elevated, by restricting the amount of food and fluid, and by gentle purgation and absolute rest. Washing out the bladder with some bland substance, such as boric acid, appears to be the best form of treatment; if there is an admixture of blood, styptics may be added, as follows:

R Liq. adrenal. (1 in 1000)	. . .	℥i (28.42 ml.)
Zinc. sulph.	. . .	gr.v (0.324 grm.)
Lot. acid. bor. ad	. . .	℥x (284.17 ml.)

To be used with an equal quantity of hot water.

Hetrazan is given in doses of 1 mgm. per kg. three times daily for seven days. After an interval a second course is taken of 150 mgm. daily for twelve days for a total of 1.75 grm.

Chylous dropsy of the tunica vaginalis, and of the peritoneum; chylous diarrhoea.—Chylous dropsy of the tunica vaginalis is not unusual in the tropics. A fluctuating swelling which does not transmit light, and which is associated possibly with lymph scrotum, with varicose groin-glands, with chyluria, or with microfilariae in the blood, would suggest this condition.

Treatment.—These chyloceles may be treated as ordinary hydroceles, either by aseptic incision or by injection. As a rule, the chylous fluid rapidly coagulates when withdrawn, but occasionally it does not, or it may be prevented by drawing the fluid off into a solution of potassium citrate.

If a minute portion of absorbent cotton is dipped into the receptacle, it will slowly fall to the bottom of the fluid. If the cotton is now picked up and placed under a low-power microscope, it will be found that every

fibre is beset with multitudes of wriggling microfilariæ entangled by their sheaths, the preparation suggesting the snake-beset Gorgon head.

Filarial orchitis with effusion into the tunica vaginalis is best treated by incision of the tunica vaginalis, turning out any clot that may be found in the sac, and stuffing the latter with iodoform gauze.

Chylous^u dropsy of the peritoneum and chylous diarrhœa of filarial origin are very rare.

Filarial orchitis, endemic funiculitis, and hydrocele.—The fever attending filarial orchitis—which is usually associated with lymphangitis of the spermatic cord—has been described as “endemic funiculitis,” but it is undoubtedly of filarial origin. It may be attended with inflammation of the scrotum, and, like ordinary elephantoid fever, resemble very closely a malarial attack. In these cases the Editor demonstrated large numbers of microfilariæ in the tunica vaginalis at the commencement of each attack. The aspirated fluid is cloudy, contains a number of polymorphonuclear cells, and occasionally erythrocytes, with microfilariæ. The epididymis is enlarged and nodular. In sections, dead and calcified filariæ blocking the vasa efferentia cause extensive fibrotic changes, and it is possible that sterility may be a direct result of this infestation.

Recurrent attacks of filarial orchitis lead sooner or later to *hydrocele*. This condition very commonly accompanies elephantiasis of the scrotum, especially among Polynesians. The walls of the sac are thickened and contain calcified remains of adult filariæ; the hydrocele fluid is clear, straw-coloured, and usually contains microfilariæ, though it does not seem to be a medium particularly favourable to them. Filarial infiltrations of the cords vary in size, form, and number. There may be one single nodule as small as a pea, or a number may be strung to thickened lymphatic vessels. Sometimes lymphatic obstruction affects the vessels so as to cause lymphangiectasis and lymphatic varicoceles; it may, however, cause cystic dilatation, or “lymphocele.” The spermatic veins are often the seat of chronic thrombo-phlebitis.

Treatment.—The living membranes of the sac can be obliterated by injection or open operation. Injection treatment is suitable for the small, flaccid, thin-walled sacs, but operation is better for the others.

Differential diagnosis has to be made from encysted hydrocele, lipoma, spermatocele, vaginal hydrocele, syphilitic orchitis, gonorrhœal epididymitis, strangulated hernia, and suppuration of the spermatic cord. Non-filarial epidemic funiculitis has been described by Power (1946) in British troops in Ceylon. This is localized induration of the spermatic cord which is due to a thrombosis in the veins. Specimens removed show a twisted mass of veins representing the whole pampiniform plexus, sometimes the thrombi break down into pus containing streptococci. It is accompanied by redness and œdema of the skin, fullness of the cord and sometimes by a small hydrocele. At first there is pain in the groin shifting to the testes with redness of the scrotal skin.

Septicæmia. Septicæmia due to *Streptococcus hæmolyticus* is not infrequent in subjects infected with *W. bancrofti*. The parent worm in the lymphatic system damages the lining of the vessels, and thus prepares the

ground for pyogenic organisms which invade the lymph-stream. In damaged lymphatic tissue streptococci find a favourable medium, enter the blood-stream, and septicæmia results.

Filarial synovitis.—Acute synovitis of the knee-joint is one of the filarial diseases, and its concurrence with filarial invasion is too common to be accidental; fibrotic ankylosis often results. Where the hip-joint is affected, removal of the inflamed iliac glands draining the area sometimes relieves the condition.

In severe cases synovitis may proceed to pus-formation, often with a fatal issue. Surgical intervention is indicated.

ELEPHANTIASIS

In certain districts in Cochin about 5 per cent. of the population, in Samoa and Tahiti about every second individual, and in Huahine seven-tenths of the adult male population, are affected by this disease. In the Ellice Islands, out of a total population of 3,484, 90 per cent. are affected. In many other tropical and subtropical countries elephantiasis, if not so common as in those mentioned, is, nevertheless, very prevalent.

The pathology of the disease is considered on p. 734.

Parts affected.—In 95 per cent. of the cases the lower extremities—either one or both—alone, or in combination with the scrotum or arms, are the seat of the disease. The foot and ankle only, or the foot and leg, or the foot, leg, and thigh may each or all be involved. The arms are more rarely attacked, though in W. Pacific this is comparatively common; out of 47 cases the arms alone were affected in 10, arms and legs in 6 cases. Still more rarely involved are the mammae, vulva and circumscribed portions of the integuments of the limbs or trunk (Fig. 202).

In any of these situations, the disease commences with a rapidly evolved lymphangitis, dermatitis and cellulitis, accompanied by elephantoid fever.

The lymphatic glands draining the affected area are generally enlarged.

There is no distinct line of demarcation between healthy and diseased skin. The implicated integuments are hard, dense, pit but slightly, if at all, on pressure, and cannot be pinched up or freely glided over the deeper parts.



Fig. 202.—Localised elephantoid tumour of groin in a Fijian.
(Dr. R. Stuppel.)

On cutting into the swelling, the derma is found to be dense, fibrous and enormously hypertrophied. The subjacent connective tissue is increased in bulk, having, especially in the scrotum, a yellowish, blubbery appearance from lymphous infiltration. A large quantity of fluid wells out on division of such tissues.

Kinmonth and Taylor (1956), by the new technique—lymphangiography—have shown that the normal lymphatic flow is maintained by spontaneous rhythmic contractility of the lymphatics. In lymphoedema and lymphatic obstruction the lymphatics are dilated and varicose and the valves are broken down.

Technique.—A diffusible dye-patent, blue V, is made up into isotonic solution in distilled water. 2 ml. is injected subcutaneously between the toes, and then massaged with gauze. The limbs are moved passively through the full range for five minutes. The dye is absorbed as high up as the pelvis. A transverse incision is made in the skin of the dorsum of the foot and it is possible to visualize the lymphatics. The lymph trunk is then injected with radio-opaque solution of 70 per cent. diodone (*pyelosil*). With a No. 18 hypodermic needle is introduced some 2 mm. into the lymphatic trunk till 10 ml. is injected. The leg is then X-rayed.

Elephantiasis of the legs. (Fig. 203).—Elephantiasis of the lower extremities is usually, though by no means always, confined to below the knee. The swelling may attain enormous dimensions and involve the entire extremity, the leg or legs attaining a circumference, in aggravated cases, of several feet.

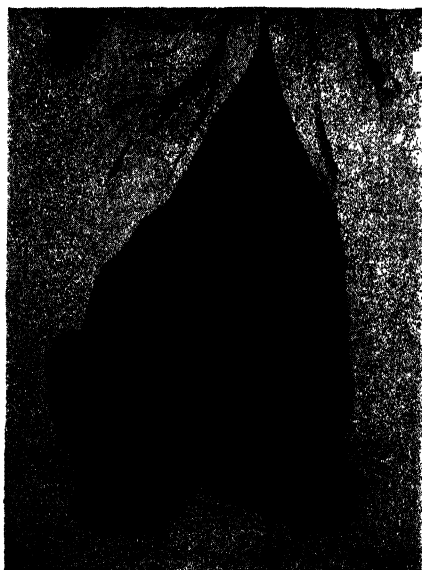


Fig. 203.—Extreme elephantiasis of legs.
(Dr. Wase-Bailey.)

Treatment.—Golden and O'Connor (1934) reported on irradiation by X-rays of lymphangitis and adenitis. Out of fifteen cases four had no further attacks. The patient should be encouraged to persevere with elastic bandaging, massage, and elevation of the limb. Swellings in the early stages may, to some extent, be controlled by elastic bandages or stockings. The latter, which should be made to fit the legs accurately, should be of some porous elastic and washable material, such as stockinette. Such a stocking (Fig. 204A) should embrace the dorsum of the foot and should accurately fit the leg to reach above the knee. Difficulty

is generally experienced with the upper margin, which extends to the thigh, as it is apt to constrict or nip the limb at this point. To obviate the pressure and discomfort of tight-fitting stockings, and to accommodate the fluctuations in the

size of the limb which necessarily take place, these stockings may be made to lace up at the sides (Fig. 204B). A spiral elastic stocking, made by Down Bros. on Dickson Wright's model, which can be accurately fitted to the leg and which is comfortable, airy and effective, can be recommended. The technique varies according to whether the leg is cylindrical, oedematous or lobulated. In the oedematous form bandaging methods should be employed. Knott is an advocate of prolonged and firm bandaging, which effects a gradual removal of the lymphoedema, during which time the patient obtains symptomatic relief and avoids further recurrent attacks of lymphangitis; the bandages should not be removed when an attack of lymphangitis is imminent, but the foot of the bed should be elevated. A "bandage boot" is used, consisting of a 6-inch bandage of heavy Turkish towelling, which covers the limb from behind the heads of the metatarsals to the heads of the tibia and fibula, cemented to a covering crêpe bandage by dextrin-syrup applied along the tibia, the whole being supported by narrow lateral strips.

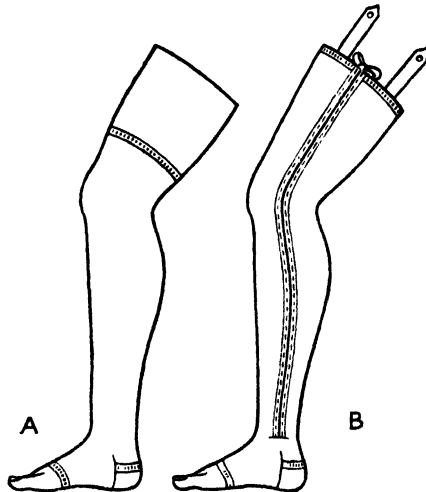


Fig. 204.—A, Plain web-elastic stocking, with foot-piece, for slight degrees of elephantiasis of leg. B, Laced form of elastic stocking, with suspenders, adjustable so as to avoid pinching. (A, James Woolley & Sons, Manchester; B, Hospitals & General Contract Co.)

Operative measures.—Sometimes in advanced cases good results follow excision of redundant masses of skin. A curved incision should be made from the head of the tibia to the ankle joint; two further incisions at upper and lower ends make a Y shaped cut. The skin is separated on both sides laterally as far as possible. The elephantoid tissues thus exposed are now incised along the whole margin as far as the periosteum and a similar incision is made parallel to this down to the muscle fascia. This separation is repeated in ring-like strips down the leg until none of the proliferated tissue remains except part of it behind the calf. Transplantation of skin and methods of plastic surgery are now being employed.

Lanz's operation aims at deep lymphatic drainage. A longitudinal incision is made through the fascia lata down to the femur, the periosteum of which is stripped and the bone trephined in several places; strips of fascia are then inserted into the openings thus made.

Kondoleon's operation consists also in free incision of the fascia lata and removal of large sections of the aponeurosis, which assists in the anastomosis of lymph channels and veins.

Auchincloss's operation is intended to lighten elephantoid legs, and also to remove those tender focal spots whence the inflammatory lesions of filarial fever arise and to excise calcified worms. It consists of two incisions marking out a vertical strip of skin. From its ends V-shaped incisions are made diverging upwards at the upper end and downwards at the lower. An almost dangerously wide amount of skin is undermined, with considerable care, just deep to the corium.

Medical treatment.—*Treatment with cortisone* (Markell and Kerrest, 1956). A trial was made with eight cases of advanced elephantiasis in Tahiti. It is argued that this hormone reduces lymphatic blockage and promotes better drainage. This treatment should be combined with bandage therapy with the addition of Unna's paste. It has the additional advantage of softening and markedly reducing the verruciform skin changes. The dose of cortisone is 100 mgm. daily, in divided doses, for a period of 30 days or longer. The total period of treatment should be 7–10 months.

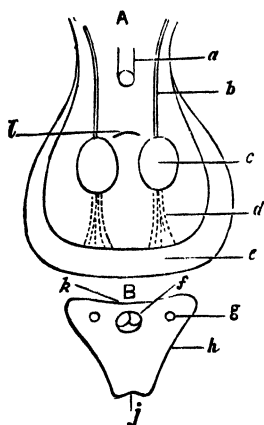


Fig. 205.—Diagram of anatomy of elephantiasis of scrotum. (For references, see text.)

Elephantiasis of the scrotum.—Elephantiasis of the scrotum or "scrotal tumour" as it is sometimes called, may attain an enormous size: 10, 15, 20 lb. are common weights for these tumours, and 40 or 50 lb. is by no means uncommon. The largest recorded weighed 224 lb.

Anatomical characters.—These tumours consist of two portions (Fig. 205): first, a dense rind of hypertrophied skin with wart-like thickenings (A, e), thickest towards the lower part and gradually thinning out as it merges above into the sound skin of the pubes, perineum and thighs; secondly, enclosed in this rind, a mass of lax, blubbery, dropsical, areolar tissue in which testes, cords and penis are embedded. The shape of the tumour is more or less pyriform. The upper part, or neck, on transverse section (B) is triangular, the base (B, k) of the triangle being in front, the apex (B, j) —usually somewhat bifid from dragging on the gluteal folds—towards the anus, the sides (B, h) towards the thighs. In the latter situation the skin, though usually more or less diseased, is, from pressure, softer and thinner than elsewhere, tempting

the surgeon to utilize it for the formation of flaps—not always a wise proceeding. The penis (A, a, B, f) always lies in the upper and fore part of the neck of the mass; it is firmly attached to the pubes by the suspensory ligament. The sheath of the penis is sometimes especially hypertrophied, in some cases standing out as a sort of twisted ram's-horn-like projection on the anterior surface of the tumour; this, however, is unusual. Generally the sheath of the penis is incorporated in the scrotal mass, the prepuce being dragged on and inverted so as to form a long channel leading to the glans penis and opening (A, l) half-way down, or even lower, on the face of the tumour. The testes (A, c), buried in the central blubbery tissue, usually lie towards the back of the tumour, one on each side—in large tumours generally nearer the lower than the upper part. They are more or less firmly attached to the underpart of the scrotum by the hypertrophied remains

of the gubernaculum testis (A, *d*)—a feature to be specially borne in mind by the surgeon. As a rule, both testes carry large hydroceles with thickened tunicae vaginales. The spermatic cords also (A, *b*; B, *g*) are thickened and greatly elongated. In spite of the grave alterations in the tissues the functions of the testes remain unimpaired.

Operation.—The patient should be placed in the lithotomy position. The scrotum should be drawn down as far as possible and elastic webbing applied over the mass so as to expel the blood; a stout rubber cord is wound round the neck of the tumour, over the pelvis, and firmly secured. A vertical incision is made, commencing in the middle of the symphysis pubis and extending as



Fig. 206.—Elephantiasis of right arm and hand in a Fijian.

far as the aperture leading to the penis. The penis is exposed, separated and the penial artery ligatured. It should be borne in mind that the prepuce and skin of the sheath of the penis have been pulled down over the glans, and form a skin-lined tube from the glands to an opening on the front of the tumour, and, while the skin of the prepuce and the sheath and even the frænum may be elephantoid, the skin of the glans is normal. At this point, a sound is passed, and left in to prevent subsequent injury to the urethra. The vertical incision is now continued round the scrotum right round to the back of the perineum, and the scrotum is thus divided into two halves. The testicles and cords are

now separated from the blubbery mass, the hypertrophied gubernacula being divided, surrounded with gauze and placed on one side. At the base of each half of the scrotum clamps are fixed, care being taken that these clamps are well to the proximal side of all diseased tissue. Each half of the scrotum is then cut away, distal to the clamps, and through healthy tissue. Every visible blood-vessel is secured and tied and the clamps very gradually loosened. The skin in the upper and inner aspects of the thigh is undermined as much as necessary and brought together over the testicles. Thiersch skin-grafts may be applied to the penis, and give good cosmetic and functional results, and, if done at the time of the operation, will take in 100 per cent. of cases. It is a good procedure to tie in a catheter until healing has taken place.

Complications which may ensue are severe hæmorrhage, and injury to spermatic cords, urethra or rectum. Postoperative retention of urine is often very troublesome. Stricture of the urethra and the supervention of elephantiasis of a previously unaffected leg have also been recorded.

Early cases of elephantiasis of the scrotum, still subject to attacks of fever with lymphangitis and cellulitis which involves the skin of the penis and scrotum, require to be handled in a different manner. In these cases enough skin should be saved to cover the testes, and the more skin taken, the less likelihood there is of a recurrence. Modern surgeons are concerned with restoration of the penis. Some take skin from the mons veneris to cover it, others from the sides of the scrotum, but this is often diseased. The scrotal suture should be as far as possible from the anus. The suture takes the form of a double cross, and a glass or rubber drain should be inserted.

Elephantiasis of the arms.—This is comparatively rare except in the Pacific. Allowing for the gravitation differences between the upper and lower extremities, the symptoms and pathology of elephantiasis of the arms are the same as those of elephantiasis of the legs. Beyond the judicious employment of massage and elastic bandaging, little can be done in treatment. (Fig. 206.)

Elephantiasis of the vulva and mammæ.—Elephantiasis of the vulva and mammæ is still rarer. Where growth has become inconveniently large, the diseased tissues should be removed. Instances are on record in which the integuments of the mammæ have become so thickened, heavy, and elongated that the organ has descended to the pubes, and even to the knees. One such tumour weighed 21 lb. after removal. Tumours of the labia or of the clitoris, similarly, may attain a great size—8 or 10 lb., or even more.

Filariasis and elephantiasis due to *Brugia malayi* (see p. 1008).—It is claimed that the clinical manifestations produced by this species differ in some respects from that produced by *Wuchereria bancrofti*. *B. malayi* is endemic in Malaya, Southern India, S. China and Ceylon, in the low-lying riverine areas, where the rivers run into the sea. The microfilaria-rate in the natives living in the vicinity of swamps is 9·8 per cent., which is about the same as the elephantiasis rate.

Adenitis is the earliest detectable lesion; inflammation of the groin-glands is frequently seen in children. Lymphangitis is also a familiar phenomenon and has a definite periodic character. Elephantiasis is of the low-grade variety, invariably confined to the legs, and is usually unilateral. The surface of the skin is usually smooth. There appears

to be great variability in the rate at which elephantoid lesions are produced. In highly infected areas it is seen in comparatively young people, especially in males, though it is typically a disease of adult life. *Microfilaria* are, as a rule, found only in 5 per cent. of cases. The absence of chyluria and the rarity of scrotal swellings have been noted in association with *B. malayi*.

Medicinal treatment of filariasis. *Antimony.*—Culbertson and Rose (1947), having demonstrated that the antimonials—neostibosan and neostam— injected into cotton rats (*Sigmodon hispidus*) will kill the adult filariae (*Litomosoides carinii*) in the pleural cavities, have applied this knowledge to human filarial infections. The first results, obtained in Puerto Rico, were rather inconclusive. The patients received 9–12 grm. of the drug over a period of 25 to 40 days. In some, two daily injections were given and in some cases the course was repeated after nine months' interval. Followed up for two years 15 out of 20 became free of circulating microfilariae. In other cases the antimony treatment appeared to have had no effect on the numbers or behaviour of the microfilariae.

Friedheim's compound T.W.Sb. (*Antimony-a.a.dimercapto potassium succinate*) has been tried out on the filariae of baboons in Equatorial Africa by Schnieder and Husson (1959) with success.

Furthermore another of Friedheim's preparations, *Mel. N.* (allied to *Mel. B*) has been tried out successfully by Friedheim, and de Jongh in Liberia on *W. bancrofti* (5 cases), intravenously, or intramuscularly in doses of 0.1–0.2, or 0.2 on 3 consecutive days. There were some allergic reactions. On the whole the results were most encouraging and from the "follow up" they conclude that this arsenical does extirpate the adult filariae.

Hetrazan (or *Banocide*), a piperazine compound, is issued in the form of the hydrochloride and the citrate. It was first tried out on the filaria of the cotton rat. Santiago-Stevenson and others then treated 26 patients with microfilaria *bancrofti* in Puerto Rico in tablet by mouth of 0.5–2 mgm. per kg. three times daily in a period lasting from three to twenty-two days. It was found that within a very short time from administration these small worms disappeared from the blood stream, but the final results on the adult worms could not be ascertained. Hawking, Sewell and Thurston (1950) have tested out antifilarial action on *Litomosoides carinii* of the cotton rat and *Dirofilaria immitis* of the dog. A marked but irregular reduction in numbers took place, but even with doses approaching the maximum tolerated, all microfilariae did not disappear from the blood. The adult worms were little affected.

Hawking demonstrated that hetrazan and its metabolic products exert no direct action on the microfilariae, but it appears to modify them in some way so that they are engulfed by phagocytes of the endothelial system and thereby removed from the circulation. In shut off cavities such as hydroceles, the microfilariae are not affected. When injected intravenously microfilariae disappear almost instantaneously.

Further reports deal with a large series of 74, including 54 males and 20 females, studied in Puerto Rico, as well as in British Guiana, the Virgin Islands and the Gambia. In the majority, regardless of *dosage*, a marked reduction in the numbers of microfilariae resulted within the space of 2–4 days after the first dose. These reductions are sustained throughout the period of treatment, but a few recurrences have been observed and

approximately one-third had negative counts from 3-6 months after cessation of treatment. Side reactions included headache, nausea, vomiting, and sometimes, skin rashes. In St. Croix, Virgin Islands, hetrazan has been made available to every inhabitant. There the incidence of *W. bancrofti* is about 20 per cent. of the population. The dosages used for 98 cases were:—

- 11 cases once daily for 5 days = 90.6 per cent reduction.
- 39 cases thrice daily for 3 days = 92.4 per cent. reduction.
- 19 cases thrice daily for 5 days = 90.8 per cent. reduction.
- 29 cases thrice daily for 7 days = 96.9 per cent. reduction.

This would indicate increasing reduction with increasing dosage and that the effect lasts about four weeks.

Hewitt and colleagues in a second report on mass treatment found that thrice daily dosage for seven days gave the best results for the whole population. In groups under control the reduction of microfilariae in the blood was about 82 per cent. and it is claimed that hetrazan provides the most practicable and convenient method for reducing the reservoir of microfilariae. In Georgetown, British Guiana, 216 patients were treated with doses from 0.2-2.6 mgm. per kg., the total dose being 13-193 mgm. per kg. At the end of treatment 95.8 per cent. of 216 were negative for microfilariae; after six months 71 per cent. and after ten 65 per cent. Total doses of less than 50 mgm. per kg. were not so effective in removing microfilariae as the larger doses, but otherwise there did not seem to be relation between dose and effect. In Uganda no significant difference has been noted in cases taking less than 50 or more than 100 mgm. per kg., and the reduction in the numbers of microfilariae in the capillary blood is 90 per cent. or over. To avoid any irritating effect on the stomach the drug is given as the powdered citrate which is soluble and pleasant to take. The accepted doses for *W. bancrofti* now is 6 mgm. per kg. (or 38 mgm. per stone of 14 lbs.) daily in divided doses of three after meals. Thus a patient weighing 12 st. should receive a total of 450 mgm. daily, in three doses of 150 mgm. each for 2-3 weeks in mild, and 3-4 weeks in acute cases.

The follow up of trials in W. Africa with hetrazan are given by McGregor, Gilles (1956). The recovery rate in a group infected with Bancroftian filariasis was higher after the lapse of three years and nine months than was registered after ten months. Of some thirty of those members of the treated group who still showed evidence of infection three years and nine months after treatment, 46.8 per cent. appeared to have maintained their original infection throughout, while 53.2 per cent. appeared to have relapsed after a period of apparent cure. The effects can be explained by the hypothesis that the active reproductive organs of the mature filariae possess a great avidity for hetrazan, so that at the time of its administration they are either killed or sterilized, and those filariae which are not mature are not affected and so survive.

The toxic effects are not serious but consist of anorexia, nausea, drowsiness, headache, and vomiting. Allergic reactions have been reported, especially in the Pacific form. When doses of 12 mgm. hetrazan citrate per kg. of the drug, given every 12 hours, the level of hetrazan base in the

blood is about 3 μ gm. per ml. The excretion in the urine is at the rate of 15 mgm. base per hour.

The treatment of *B. malayi* with hetrazan is the same as for *W. bancrofti* but the resulting allergic reactions are said to be more severe (Hawking, 1950).

Antrypol (or Suramin).—Thooris (1956) has given this drug intravenously—1 gm. weekly, for seven weeks in sufferers from lymphangitis and carriers of microfilariæ. Systemic disturbances were much reduced and the conclusion reached that it exerts a definite antifilarial action.

Arsenicals. *Sodium thiacetarsamide* (arsenamide).—Otto and Maren, 1950; Hawkins, 1951—is administered intravenously for 15 daily doses, which appears sufficient to completely eliminate microfilariæ in patients suffering from the non-periodic type (*W. bancrofti* var. *pacifica*) (Otto and others, 1953). After injection there is an actual increase in the number of microfilariæ for it acts on the uterus of the adult female causing a sudden discharge of embryos. In some of the patients treated with this drug in 2 per cent. solution, in doses of 1.0 mgm./kg. for 15 days, microfilariæ were absent from the peripheral blood after an interval of two years, indicating the probable death of the adult worm or worms.

McFadzean and Hawking have tried arsenamide on 32 patients in the Gambia. The dosage is 125 mgm. (1.8–2.5 mgm. per kgm.) daily by intravenous injection usually for 10–12 doses. It removed the greater majority of the microfilariæ of *W. bancrofti* from the blood in two weeks, and all, save two, remained free from microfilariæ for six months. From this it is concluded that the treatment either killed or sterilized the adult worms and exterminated the majority of the microfilariæ at the same time. The disadvantage is the toxic action, especially on the liver. One patient died of hepatic necrosis after the third injection.

Prophylaxis of filarial disease.—The prevention of filarial disease resolves itself into anti-mosquito measures and protection from mosquito-bite. Unprotected wells, tanks, cesspits or stagnant pools must not be permitted in the neighbourhood of dwelling-houses. All vessels used for storing water should be emptied at least once a week. The mosquito-net is indispensable in filarial as well as in malarial countries. In the Pacific Islands, especially in the Gilbert and Ellice group, considerable reduction of filarial incidence has taken place following O'Connor's recommendation to cut down the thick undergrowth, thus giving passage to the Trade Winds which blow away the mosquitoes (*Aedes scutellaris polynesiensis*). Burning empty coconut shells and filling up holes and cavities in the trunks of the coconut trees has been beneficial, as it destroys breeding places. Destruction of rats (*R. rattus*) which nest in the coconuts and bore holes into the nuts, thereby creating ideal breeding places, must be carried out.

Active measures are now being undertaken in Tahiti and Fiji and other Pacific islands to combat filariasis, by spraying with DDT, bush clearing and prophylactic administration of hetrazan. The training of special anti-filarial teams, as in Fiji under D. W. Amos, is a practical method of great importance. In the island of St. Croix, West Indies, the U.S. Public Health Service introduced residual insecticide methods against *Culex tafigans* and *Aedes ægypti*. The best method was found to be DDT-Xylene-Triton emulsion (85 per cent. DDT-Xylene concentrate with

Triton X-100 diluted with water to form a 5 per cent. spray). In all 11,078 houses were sprayed each on four occasions. The result was a 50 per cent. reduction of *C. fatigans* whilst *A. ægypti* seemed to have disappeared (Kohler, Brown, and Williams).

Mass treatments with hetrazan have been instituted in the Virgin Islands, Tahiti and elsewhere with the idea of banishing microfilariæ from the peripheral blood, thus breaking the chain and rendering mosquito transmission impossible. The most detailed campaign so far conducted is by McGregor, Hawking and Dean Smith (1952) in the Gambia. Hetrazan citrate was given in 25 mgm. per kg. for five days. Of 154 infected persons 64 per cent. had their blood free from microfilariæ for 10 months, and in the remainder the parasitæmia was substantially reduced. These doses were not well tolerated. Beye, Kessel and colleagues (1953), in mass treatment in Tahiti, also succeeded in reducing the microfilarial density after two hetrazan courses of seven days each, but after two years the effect was not so striking, though the "larva index" in *Aedes scutellaris* mosquitoes has been reduced to one tenth.

In *W. bancrofti* filariasis, in which the periodicity is nocturnal, and where night-biting mosquitoes, such as *Culex fatigans* and *Anopheles*, are concerned in transmission, the disease should be treated as a house-infection by sanitary measures and DDT sprays which, in this respect, have been eminently successful.

Iyengar (1937) conducted a successful campaign against the intermediary mosquito of *Brugia malayi*—*Mansonioides annulifera*, and the water lettuce *Pistia stratiotes*, to which the larvæ become attached, and succeeded in clearing this plant from North Travancore, with the consequent elimination of filariasis from that area. The species of *Mansonioides* which act as vectors in Malaya flourish in association with the roots of swamp trees. The methods adopted in Travancore, therefore, cannot be applied to Malaya. The control of *P. stratiotes* in Ceylon by herbicides is efficiently performed. The best are Phenoxylene 80 and Shell Weedkiller D. (Dassanayake and Chow).

Epidemiology of filariasis.—The natural infection rates of mosquito intermediaries vary considerably and do not form a true index of the risks of contracting filariasis in endemic areas. In Malaya it is now recognized that the majority of larval filariæ in wild-caught *Mansonioides* are of avian or mammalian origin so that Edeson and colleagues have now abandoned the natural infection index as being the true token of human filariæ endemicity. In recent years high natural infection rates have been recorded. Iyengar in the Cook Islands made it 13.5 per cent., and Gaillard in Tahiti as high as 50 per cent. Symes in Fiji found the natural infection rate of *Aedes fijiensis* as 21.6 per cent. It is quite probable now that the majority of these infections are derived from avian blood, because these mosquitoes feed mostly on birds. In the case of *Aedes s. pseudoscutellaris* and *A. s. polynesiensis* both feed on dogs and are capable of transmitting *Dirofilaria immitis*, the filaria parasite of the dogs. There appears to be no reliable method of distinguishing different species of filariæ during their larval stages at present (see p. 1006).

The subjects of filariasis should be regarded as dangers to themselves and to the community, and be compelled to sleep under mosquito-nets.

II. FILARIASIS DUE TO LOA LOA (LOIASIS)

History and geographical distribution.—The embryonic form (microfilaria diurna), which closely resembles microfilaria bancrofti, was described by Manson in 1891; the patient from whom the specimen of blood was derived had formerly had an adult *Loa loa* in his eye. Later, association was established between *L. loa* and the disease known as Calabar swellings, and also between that disease and microfilaria diurna.

Loa loa is widely distributed in West Africa from 8° N. to 5° S. of the equator from the Gulf of Guinea eastwards to the Great Lakes. It is especially common in the Cameroons and on the Ogowé River; its distribution is, however, mainly confined to the coastal plains, and follows the course of the Congo and its tributaries to a point about 1,500 miles from its mouth (Map XII). This parasite is also found in the Southern Sudan between the Bahr el Ghazal and the Belgian Congo between latitudes 4° and 6° N. and longitudes 27° and 31° E.

Ætiology.—A description of the adult *Loa loa* is given in the Appendix, p. 1012. Here it suffices to say that it is 30 mm. or more in length, the female being, as a rule, considerably longer than her partner (Fig. 207). The cuticle is embossed with numerous characteristic protuberances. Gordon and Duke have shown that *L. loa* infests forest monkeys in the Cameroons, and that similar species are peculiar to these primates.

Structure of the embryonic form.—Microfilaria loa (= diurna) is very similar in size (298 μ by 7.5 μ) and structure to microfilaria bancrofti. Like the latter, it is enclosed within a "sheath," its tail is pointed, and it has similar V- and tailspots. (Fig. 185, 2, p. 724.)

The periodicity is the exact reverse of that of microfilaria bancrofti, for the embryos appear in large numbers in the peripheral blood during the daytime and disappear at night. The periodicity is, in fact, diurnal (Chart 29).

The respective periodicities are very characteristic—more so, apparently, in microfilaria loa than in microfilaria bancrofti; for, whereas by inverting the sleeping habits of a subject of *W. bancrofti* infection it is easy to invert or disturb the periodicity of the microfilariae, this has not been done so easily with microfilaria loa, although several experiments have been made. It does, however, take place gradually, as for instance when the patient travels round the world (Külz, 1914). In Americans who have been infected in West Africa, the microfilariae maintain their periodicity on their return home. A series of important observations on the mechanism of periodicity were made by Gönnert, who was transfused with blood from a patient heavily infected with *L. loa* and *D. perstans*, whose blood contained 1,640,000 of the former and 112,000 of the latter per 160 ml. Subsequently, microfilariae loa were demonstrated in the recipient's blood and maintained a strict diurnal periodicity for three days. Most of the microfilariae perstans disappeared from the blood within the first few days, but some persisted for at least three years.

Life-history.—In early editions of this work Manson called attention to the



Fig. 207.—*Loa loa*.
Nat. size.

and it has been excised from under the skin of the back, from above the sternum, from the left breast, the lingual frænum, the loose skin of the penis, the eyelids, the conjunctiva, the anterior chamber of the eye, and also the scalp. The parts most frequently mentioned are the eyes, and, although the worm may attract more attention in this situation, it does seem as though it had a decided predilection for the eye and its neighbourhood (Fig. 208). A patient of Manson's once stated that the average rate at which a loa travelled was about an inch in two minutes. Both he and others have observed that warmth, such as sitting before a fire, seems to attract them to the surface of the body. Chesterman on the Congo reported finding live adult worms in 10 per cent. of all cases operated upon for hernia and elephantiasis while cretified worms, too, were frequently encountered. Whether alive or dead, this parasite evokes a high eosinophile response, and an increase to 80, 40, and even higher percentages, is common in Europeans who have resided in the endemic districts in Southern Nigeria, the Congo and Cameroons. Occasionally, as in one patient, who had manifested Calabar swellings over a period of seven years, all adult filariæ appeared to die out at the same time and were discharged in a calcified state from minute chronic abscesses which appeared on the hands, arms and legs.

Symptoms.—As a rule, the migrations of the parasite give rise to no

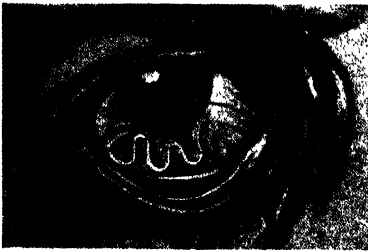


Fig. 208.—*Loa loa* in the eye.
(After Fülleborn.)

serious inconvenience, but they may cause prickings, itching, creeping sensations, neuralgia and, occasionally, transient cedematous swellings (Calabar swellings) in various parts of the body. When the parasite appears under the conjunctiva it may cause a considerable amount of irritation and congestion; there may even be actual pain, associated with swelling and inability to use the eye and, perhaps, tumefaction of the eyelids (Fig. 209). Should a loa wander into the rima glottidis, or the urethra, the consequences might be serious, and great pain is sometimes caused. Occasionally, too, as Chesterman recorded, the death of the parent worm may cause a localized abscess in the groin or axilla.



Fig. 209.—Calabar swelling of right eye. (Orig.)

There is some evidence that occasionally the adult worms may enter the central nervous system and cause cerebral symptoms. Bonnet (1943) described a fatal case of meningitis with microfilariae in the cerebro-spinal fluid and Kivits (1954) four cases of encephalitis with similar findings. These may have been coincidental, but Peruzzi and Lavier, working with monkeys, found adult filariae near the medulla and in the cervical grey matter. Browne (1954) has given a graphic description of cerebral disturbance in a woman in the Congo who had been infected for 25 years. There was hemiparesis of the left side of the face with extensor response of the left plantar reflex. The left arm showed constantly slight dysidiadochokinesia. The left optic disc was blurred. All these symptoms and signs were transient.

CALABAR SWELLINGS

The swellings are about the size of half a goose egg, painless, though somewhat hot, both objectively and subjectively, not pitting on pressure, and usually disappearing in about three days. They come suddenly and disappear gradually, and occur in any part of the body. They may irritate slightly but the skin maintains its normal colour. One swelling occurs at a time, but recurs at irregular intervals and, perhaps, for many years after the patient has returned to Europe. In some instances the swellings seem to be due to rubbing provoked by the irritation accompanying the presence of a loa just under the skin; in other instances they develop spontaneously. In Johnstone's own case a localized Calabar swelling appeared round the worm as it lay coiled up in the outer aspect of the upper eyelid. In the hand or forearm they may give rise to a sensation of powerlessness and soreness, as if the part had received a blow. They never suppurate (Fig. 210). The effects of temperature upon these swellings is important. During the hot summer months they are most frequent: in the cold weather distinctly uncommon.

Although in a large proportion of cases, *L. loa* embryos cannot be found, in a number of others, either the parent worm has shown itself in the



Fig. 210.—Calabar swelling on dorsum of hand in a European lady from the Congo. (Orig.)

eye, or its microfilariae have been detected in the blood. This discovery, together with the geographical endemicity of these swellings and their clinical characters, makes it practically certain that they are produced by *L. loa*. Manson believed that the swellings might be caused by the emission of her larvae by a parent loa into the connective tissue, but it was proved by Fülleborn that they represent an allergic reaction on the part of the tissues in response to filarial toxins, and so can be reproduced by injections of extracts of the adult filariae.

The recurrence of Calabar swellings on the arm or leg appears to give rise to induration of the fascia and connective tissue round the tendon-sheaths. In two cases the Editor observed permanent circular cyst-like swellings which may cause pain on muscular movement. Solid oedema of one leg persisting for six weeks has been observed in a European from West Africa who had been infected for a number of years; hydroceles also have been recorded (Fig. 211). Kivits (1958) has drawn attention to neuritic pains especially in the arm which are accentuated by treatment with hetrazan. Numbness has been noted in the middle two fingers accompanied by oedema and hypoesthesia. It is suggested that these manifestations represent an allergic reaction due to the death of the adult *L. loa*.

Urticaria and dermatitis of a particularly irritating form with pruritus are sometimes found in filaria cases. The dermatitis is analogous to that found in onchocerciasis. As, in infections with *W. bancrofti*, multiple intramuscular abscesses, due to secondary invasion by staphylococci or streptococci, and even infections of the hip-joint, may sometimes be found in association with *Loa loa*.



Fig. 211.—Hydrocele and solid oedema of right leg in *L. loa* infection from West Africa. (Orig.)

Diagnosis.—The microfilariae can be demonstrated in the blood, or the high eosinophilia (80–60 per cent.) suggests this parasite. Confirmatory evidence can be obtained by the intradermal or complement-fixation tests (pp. 735, 736). An antigen is prepared from the filariae of the South American ostrich (*Contortospiculum rheæ*), from the filaria of the cotton rat (*Litomosoides carinii*) or *Dirofilaria immitis* of the dog (see p. 736).

Treatment.—Calabar swellings are notoriously difficult to treat effectively. The irritation can best be allayed by evaporating lead lotion,

or by *heliobrom* (dibromotannate of urea) in alcohol. Fairley employed a desensitization method with increasing strengths of *Dirofilaria* antigen, from 0.5 ml. of the extract in normal saline, gradually increasing to 5 ml. or more, and he had some success.

Hetrazan.—Murgatroyd and Woodruff treated 17 Europeans in a series in which the infections had lasted from 1–24 years.

The dose was 2 mgm. per kg. three times daily lasting 10–21 days with total amounts of 1.2–10.5 gm. Morbilliform and urticarial rashes ensued, alleviated only by benadryl and anthisan. In these serpigenous/linear swellings due to adult worms appeared under the skin. The results were favourable and dead filaria were extracted from skin nodules. The filarial skin test remained positive, whilst in a small number the complement fixation test became negative.

Schneider (1950) treated a much larger series of 71 patients with daily doses for males of 0.4 gm. and 0.8 gm. for females for a similar period. Allergic reactions were frequently encountered in some 70 per cent. These were pruritus, fugitive erythemata, Calabar swellings and creeping sensations beneath the skin. All these reactions responded satisfactorily to anti-histamine drugs.

Woodruff (1951) has shown by liver biopsy that, as in the case of filarial infections of laboratory animals with *Litomosoides carinii*, the microfilariae quickly disappear from the blood and are destroyed in the liver after treatment with hetrazan.

Diagnosis of microfilariae in thick films.—It has been pointed out by Golvan (1956) that in old thick drop blood preparations microfilariae of *L. loa*, *W. malayi* and the new species, *W. bancrofti* var. *vauceli* have a shrunken appearance while microfilariae of *W. bancrofti*, *W. bancrofti* var. *pacifica*, *Mansonella ozzardi* and *D. Dipetalonema perstans* do not. This is due to the greater permeability of the cuticle in the former group which permits fast drying and more rapid staining. Whatever the methods of staining microfilariae of *W. bancrofti* become shorter, their width increases and this feature suffices to identify them. Microfilariae do not shrink in the same way. In *loa-malayi-vauceli* group the nuclear column follows the winding of the cuticle, while in *bancrofti* the nuclear column is twisted inside the wrinkled cuticle.

III. HUMAN ONCHOCERCIASIS

History and geographical distribution.—*Onchocerca volvulus* was originally discovered by a German medical missionary in negroes of Ghana and the parasite was named *Filaria volvulus* by Leuckart in 1893. Blanchard, in 1899, demonstrated that it lay in a lymphatic space in a tumour. It occurs sporadically throughout the whole of the Congo basin, but especially on the Oellé, Kibali and Itimbiri rivers, Chad area, and along the Mayo Kebbi river in French Equatorial Africa. It is estimated that over 200,000 persons in French W. Africa are infected. The three main areas are Upper Volta, Sudan and N. Dahomey. In Owbangi Chari there is a heavily infected area and a new locality in Aden Territory has been discovered by Fawdry (1956). The most southerly focus is Katabola 13°

South. It is absent from Mozambique (E. Africa), but recently it has been detected in Ethiopia (Jimma, Kaffa-Gore). It has also been introduced into the Island of Fernando Po. It has been observed in Nigeria, in the Cameroons, in Senegal and French Guinea, in Uganda, in Togo, Dahomey and Ivory Coast, on the lower reaches of the Volta river in Ghana, in Kenya (Kakamega and Southern Kavirondo), in Tanganyika, in Nyasaland, and in the Southern Sudan (Bahr-el-Ghazal) (Map XII).

In 1915 Robles described *O. volvulus* as being common in Guatemala. Caldéron (1920) defined the endemic zones as being in the departments of Sacatapéquez, Escuintla, and Solola, at an altitude of 2,800–3,600 ft. It is suggested that the parasite was imported by negro slaves from Jamaica, though Brumpt classified the S. American worm as a distinct species—*O. cæcutiens*, “the blinding filaria”—mainly on account of its association with a curious punctate keratitis, minor distinctions in the morphology of the male parasite, predilection of the tumours for the head, and endemic zone of the disease at an altitude of 600–1,200 metres. De la Torre described onchocerciasis in Mexico, over 15,000 cases in the State of Chiapas and 5,000 in Oaxaca being known. On the other hand, Strong, Sandground, and Bequært (1934), in their monograph on onchocerciasis in Central America, demonstrated that *O. volvulus* and *O. cæcutiens* are morphologically identical. In Guatemala, onchocerciasis occurs endemically in those districts in which coffee is grown, from 2,800–3,000 ft., especially amongst the Indian population. Hyperendemic, heavily endemic and lightly endemic areas are recognized, the exact degree being determined by the incidence of the disease in children, together with that of blindness.

Ætiology.—The worms are white and filiform, tapering at both ends. They vary considerably in length, the female, as in all the filariæ, being much the longer (35–40 cm.). At least four males and two females are present in every tumour. The unsheathed embryos measure about 300 μ in length. Macfie and Corson found that in the Gold Coast natives microfilariæ are commonly encountered in sections of the skin, but some of the embryos, they believe, are referable to a new species, *Dipetalonema streptocerca* (see p. 1018), distinguishable from those of *O. volvulus*. The presence of the microfilariæ of *O. volvulus* in the skin is associated in some with a lichenoid condition.

Life-history.—Embryos, presumably those of *O. volvulus*, have been found in the peripheral circulation by Fülleborn, Simon, Ouzilleau, and Rodenwaldt; but usually the microfilariæ occur round the periphery of the tumours, and are ingested by the jinja-fly (*Simulium damnosum*), in the thoracic muscles of which they undergo a development similar to that of *W. bancrofti* (Blacklock). In Kenya the species is *S. neavei* (Buckley), whilst in South America the insect intermediary hosts are *Eusimulium avidum* (*metallicum*), *E. ochraceum* and *E. mooseri*.

Gibbins and Löwenthal showed that in Victoria Nyanza district of Uganda distribution of cutaneous onchocerciasis amongst the natives coincides with that of *Simulium damnosum*. In the Red Volta district the fly incidence is 13 per cent. and the rate of infection amongst the different age groups is given as 38 per cent. under 10 years, 91 per cent. in the next decade and beyond that 100 per cent! Onchocerciasis begins in childhood as early as the first year of life. The presence of this dire disease obstructs all forms of economic development and has led to depopulation. Thus the people of the Mayo Kebi Valley in French Equatorial Africa deserted their territories on account of the high percentage of blindness.

Pathology and symptoms.—*O. volvulus* is found in peculiar subcutaneous fibrous tumours, the size of a pea to that of a pigeon's egg. The same patient may present one or several of these tumours (Fig. 212). The regions of the body most frequently affected are those in which the peripheral lymphatics converge. Thus, the tumours are usually found in the axilla, in the popliteal space, above the elbow, in the suboccipital region, and in the intercostal spaces. In their incipient stages they cause very considerable pain. Periodic recurrences of symptoms are attributable, according to native belief, to the lunar cycle, occurring almost



Fig. 212.—*Onchocerciasis* from the Congo.
Typical nodules on knees, elbows and scalp.
(Dr. C. C. Chesterman.)

every fifteen days. In the South American form the occipito-frontal and temporal regions are most usually affected. Strong found in Ste. Emilia, Guatemala, 54 per cent. of the inhabitants infected.

The tumours are situated on the head, usually the scalp, and measure 6–20 mm., rarely as much as 30 mm. They may cap the skull, and from them the adult worms may be obtained entire by digesting the tissues with papaya juice, or papaine, in 0.2 per cent. HCl. The tumours are never adherent to the surrounding structures and can be easily enucleated. They are formed of a dense mass of connective tissue, which enwraps the parasites and encloses small cyst-like

spaces filled with a greyish viscous substance consisting almost entirely of microfilariae. The position of the adult worms within these tumours is very remarkable. The greater length of the coiled-up bodies of the females is embedded in the connective stroma; consequently they can only be extracted in fragments.

Chesterman believes that the distribution of nodules is correlated to that of the lymphatic vessels, on anatomical grounds. Thus there is an absence on the

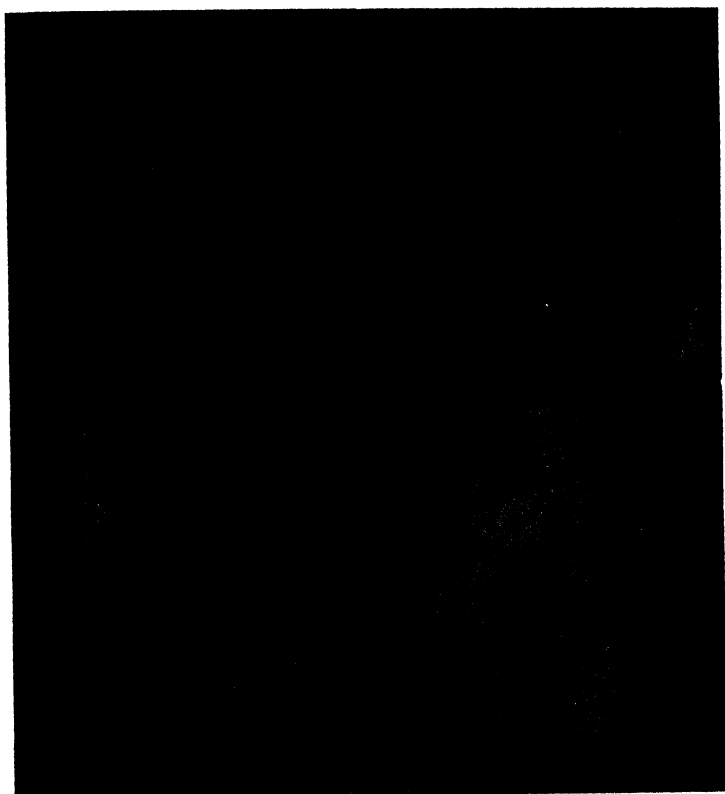


Fig. 213.—Lichenoid eruptions of onchocerciasis. (After Fülleborn.)

“lymphshed” between the vessels that pass to axillary and lymphatic glands, and a correspondence between the commoner sites with terminal aborigations of the cutaneous lymphatics. This seems to suggest that the developing female worms travel up them from the lymph glands till their diminishing calibre arrests further progress. Also nodulation frequently occurs in old scars with presumably interrupted lymph channels.

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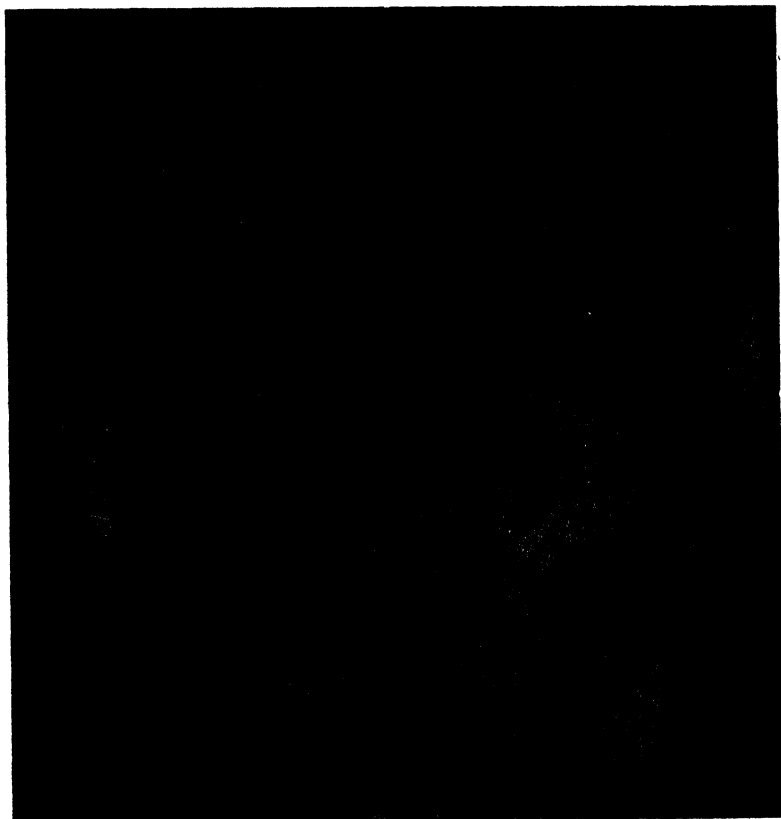


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inguinal hernia and at Cæsarean section. Though they are most commonly found in adults of mature years, Strong saw *volvulus* tumours in a child of two months, and found that they often give rise to neoplasms. Sometimes, however, especially in Europeans, the embryos may exist in large numbers in the skin without any palpable nodules. Indeed recent experience has shown that they may occur in large numbers in normal skin in infected subjects (Fig. 214).

Robles reported that tumours of the scalp and periosteum may produce epileptiform attacks in Colombia, due to perforation of the cranium. Erysipelatoid skin-rashes (known as "*Erisepela de la costa*") are common

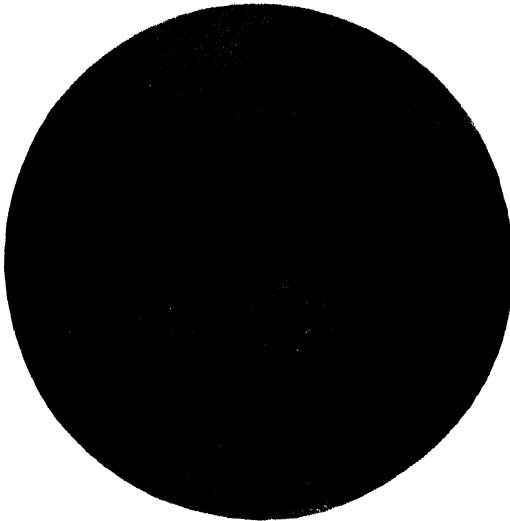


Fig. 214.—Microphotograph of microfilaria of *O. volvulus* in subcutaneous tissue. Note absence of tissue reaction.

(Photograph by Dr. P. H. Martin.)

in the South American form. Sometimes pressure symptoms are produced and sometimes also epilepsy appears to be caused by microfilariae in the cerebral cortex (Gopsill, 1939).

Lymphatic enlargement of the scrotum, hydroceles and enlarged testes were noted by Dyce Sharp in patients infected with *O. volvulus*, while the embryos can be demonstrated in hydrocele fluid, as well as in cedematous lymphatic tissue. On the Congo, Ouzilleau and Chesterman have described elephantiasis of the scrotum and legs in association with this parasite (Fig. 215). As in *W. bancrofti* infections, localized abscess formation also occurs, and several dead female worms have been removed from them. The elephantoid scrotum due to *O. volvulus* is convoluted like a brain, or like a wrinkled walnut shell, and the subcutaneous tissue is more solid and less cedematous than that in elephantiasis attributed to *W. bancrofti*, while the embryos are found in the skin.

The restricted localization of elephantiasis appears to be related to the position of the nodules. This may possibly explain its absence in the American zones of endemicity, as the nodules there are located principally above the shoulder and are there not in a position to produce genital elephantiasis. Moreover the vector, *Simulium damnosum*, prefers to bite the lower half of the body, while *S. neavei* behaves differently and in Uganda it attacks the head, feet and legs. Elephantoid deformity of the face may ensue. The cedema is so gross that the orbits become obliterated. The nose becomes tuberoso and the whole appears as a ludicrous caricature



Fig. 215.—Section of *Onchocerca volvulus* nodule, showing adult worms in skin at various levels. $\times 76$. (Wanson, 1950.)

of the human countenance. In Mexico *S. ochraceum*, the vector, bites predominantly on the head and neck, the sites where the nodules most commonly occur.

The "hanging groin"¹ has been described by Nelson (1958) in all heavily infected areas in Uganda and in the endemic foci in Kenya in long-standing cases (Fig. 216). The skin sac contains enlarged, sclerosed femoral or inguinal lymphatic glands in a matrix of connective and lymphoid tissues. They are not hernias, but predispose towards them. They are not elephantiasis. The hernial sac is attached by fibrous adhesions to the sclerosed glands. They are quite characteristic and occur in those regions in which the microfilarial concentration is highest.

Van den Berghe recognizes several varieties of nodules—those with eggs; those with free microfilariae; those with greenish, syrupy or caseous pus; cold abscesses full of pus and remains of worms and fibroid nodules without eggs or microfilariae.

¹Also known as "Pseudo-Hottentot Apron" in women.

Déjou (1939) described acute arthritis in onchocerciasis in French West Africa. Microfilariae can be demonstrated in the synovial fluid obtained by joint puncture, which should be examined soon after withdrawal. In these cases filarial nodules can be found in the cruro-inguinal region, in the popliteal spaces, and on the costal margins.

Skin symptoms.—Dermatitis (xeroderma) or lizard skin (Rodhain and Dubois) is commonly associated with *O. volvulus*. The skin affection is described by some as *lichenoid* and is more easily visible on the back (Fig. 213). It is usually seen in South American cases, but shows up much better in Europeans than in dark-skinned natives. The skin is



Fig. 216.—Hanging groins in onchocerciasis. (E. S. Smith, Lagos.)

thickened as well as wrinkled, as Fülleborn described in German colonists from Mexico. This complication was termed *lichen* by Macfie and Corson and *scleroderma* by Ouzilleau in West Africa.

Recurrent inflammations of the skin of the face often result in enlargement of the pinna of the ear. Associated with this there is a definite dermatitis, with discoloured patches of skin on the neck and back, and xeroderma, especially of the elbows. The patient experiences terrible pruritus, especially at night. Quite commonly he suffers from photophobia and some aberrations of vision. Usually there is an eosinophilia of about 35 per cent.

Several onchocerca nodules can usually be found in the deep subcutaneous fascia, and when excised, the adult worms can be demonstrated.

Eye lesions.—Kershaw in the Cameroons and in N. Nigeria found, by counting the number of microfilariae in skin snips, that the numerical distribution had a clear pattern which was related to the extent and severity of the skin lesions as well as to the ocular changes and blindness. Onchocerciasis in W. Africa is not uniformly associated with blindness.

In Northern Ghana it is estimated that 40,000 are blind from the disease. In Nigeria and the adjoining French territories it is also a very serious problem.

The ocular manifestations are very frequent. Lesions of choroid and retina are serious, but lesions involving the anterior segment of the eye are most frequent.

The conjunctiva may contain numerous microfilariae of *Onchocerca volvulus* and sometimes they are found in cases in which these parasites have not been found in skin snips taken from different parts of the body.

It is difficult to know how it comes about that in some patients the microfilariae do not cause any apparent reaction or lesions in the conjunctiva: in others however they may cause chronic conjunctivitis with hyperæmia, thickening and absence of conjunctival secretions. Small nodules, about 2 mm. in circumference, red in colour, form at various distances from the limbus and especially in this region they are the most characteristic and numerous whence they find their way into the anterior chamber. Owing to phototropism of the microfilariae they abound in the area uncovered by the eyelids. The conjunctiva in this region forms a rampart 2-3 mm. in thickness, red in colour owing to dilated blood vessels, and studded with minute brown spots, most commonly seen in Africans. The most typical corneal lesion is chronic avascular nummular keratitis situated at the periphery of the cornea and so causes little visual disturbance until it has progressed to the centre (Fig. 217). This keratitis may persist for years and leave permanent opacities which seem to be due to the presence of microfilariae. Photophobia, lacrymation and blepharospasm are the result.

With the aid of the corneal microscope living microfilariae are rarely seen in the cornea, but when dead they may be distinguished, sometimes in considerable numbers. They are usually white and

rectangular, lying parallel to the corneal surface. The aqueous humour of the eye contains numerous microfilariae which are very active. They may equally well be observed in the aqueous humour by the use of the electric ophthalmoscope with a plus 20 to plus 28D lens, held 3.5-5.0 cm. from the centre of the anterior chamber. The microfilariae can then be seen in silhouette as small black threads swimming through the humour. This method is, of course, better adapted to conditions in Central Africa.

Disintegrating microfilariae may form a false hypopyon, light brown in colour, at the bottom of the anterior chamber. This results in the pupil becoming pear-shaped which is characteristic of this disease.

Iritis of the plastic type is not a common feature, but diffuse atrophy of the iris may often be seen. At first the surface is smooth, but then it becomes dull, the pigment disappears and it resembles a sponge and is known as the "pumice-stone iris." Cyclitis is indicated by the presence of precipitates occurring more frequently than iritis and may develop with secondary cataract and glaucoma. Cataract is common in those over 40 years who show filarial lesions, and has been seen in children.

Infections of the vitreous may occasionally occur. Choroido-retinitis is manifested by varied signs. Pigmented patches alternate with white patches of choroidal atrophy. The small spots have the appearance of

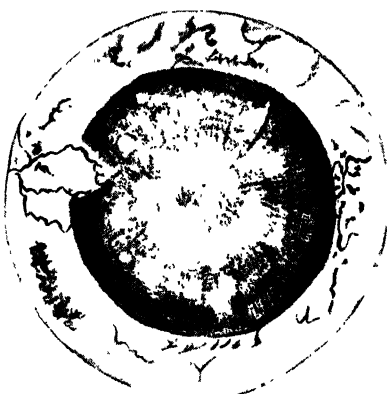


Fig. 217.—Ocular onchocerciasis from the Congo, showing punctate keratitis and lateral formation of pannus. (Hissette.)

fine powdered salt on a red background, the larger spots have sharp margins white or yellow in colour, often in clusters resembling bunches of grapes and in close proximity to the blood vessels. Retinal lesions are rare, and many pigmented patterns which have been described have been found by Choyce to be racial peculiarities. This also applies to what are known as primary and secondary optic atrophies which are now thought to be due to other causes. In S. America optic atrophy is rare (Toulant and Bothias).

Periarterial thickening appears to be due to the penetration of micro-filariae into the sheaths of the central blood vessels.

Some modern ophthalmologists believe that *O. volvulus* can only cause blinding lesions of the anterior segment of the eye (Choyce, 1958).

The greater the distance between the eyes and the localization of the adult parent filariae, the longer is development of eye lesions delayed. These ocular lesions are more common in those with nodules near the eyes.

Diagnosis.—The diagnosis is made by snipping off a piece of skin with forceps near a nodule, placing it in saline solution for 15 minutes at 37° C., centrifuging and then pipetting off the bottom layer with the microfilariæ which have escaped from the tissues. This little operation can be painlessly performed by inserting a small hare-lip needle under the skin and snipping off the superficial layer. The embryos are thermotactic, and are attracted by heat to the surface of the skin; thus, demonstration is best effected by placing hot fomentations on the skin, and then taking off shavings by means of a Thiersch razor. When these are placed in warm physiological saline, embryos can be detected. Reliance should not be placed on a single biopsy. It may be necessary to take as many as five before a positive finding is obtained. Scarification of the skin is a more convenient procedure for field surveys. Howard recommends placing a powerful electric light bulb a few inches from the skin. No local anæsthetic must be used, and freezing is especially contra-indicated. In the eye Ridley recommends the examination of snips of the conjunctiva under cocaine anæsthesia. A portion of the bulbar conjunctiva is seized with toothed forceps and abscised with scissors. Conjunctival biopsies are more often positive when skin biopsies are negative.

Intradermal tests.—These tests were carried out by Fülleborn, Rodhain and Dubois with dirofilaria antigen (*see p. 795*). The results have not been as satisfactory as in other filarial infections. The antigen should be diluted 1 : 2000 (White and Murdock).

Complement-fixation reaction in onchocerciasis.—Van Hoof employed a complement-deviation test for onchocerciasis, based upon the same principles as other similar tests in filariasis, and he considered that it had done much to remove uncertainties regarding the pathogenic action of this parasite.

The tightly-packed mass of adult parasites is retained when dissected out of the cyst. The filariæ are then cut into thin slices and placed in a desiccator over sulphuric acid, and when dry they are extracted with ether at 25° C.—a process which occupies several days—and are subsequently dried and extracted with alcohol for ten days. The best extracts have an antigenic titre of 1 in 25. It is claimed that the test when put up by the Calmette-Massol technique is

so specific that neither *Loa loa*, *A. perstans*, nor intestinal helminths are able to vitiate it. The antibodies thus demonstrated are present in serum, cerebrospinal fluid, synovial fluid and oedematous exudates.

The observations so far made on the positive reactions by this test are in favour of the view that certain forms of elephantiasis in the Congo are manifestations of onchocerciasis.

Eosinophilia is not usually marked in onchocerciasis and is therefore not useful as a diagnostic sign.

Treatment.—In the African form the tumours appear to be painless, and may be removed by excision. In the South American form, removal of the tumours under cocaine anæsthesia is said to be followed by an improvement in the ocular conditions within a week or so. Adams (1938) stated that in a European from the Katanga province of the Congo intravenous injections of neostibosan arrested progress of the corneal opacities, but, in comparable cases observed by the Editor, no improvement was noted, so that antimony therapy had to be discontinued. Harris, who gave sodium antimony tartrate intravenously, noted that the microfilariae disappeared from the skin, in some cases rapidly, when the treatment was continued over a period of four weeks. A useful application to alleviate pruritus is *heliobrom* (dibromotannate of urea) 10 per cent. in spirit, applied to the skin at night.

Hetrazan.—Stoll says that it has a specific and rapid action. The side reactions are common, frequently serious, allergic in character, but of short duration. Herxheimer-like reactions have been recorded with large doses, and are probably due to massive destruction of microfilariae. In Africans, especially, hetrazan evokes the most intolerable skin reactions and, moreover, serious loss of visual acuity may result from iridocyclitis. Mazzotti and Hewitt state that the most convenient dose is 2 mgm. per kg. three times daily for 21 days; but where the infection is heavy they commence with $\frac{1}{3}$ of the daily dose for the first day, $\frac{2}{3}$ for the second day and the full dose for the third. It should be given after meals. Should allergic manifestations become severe it is advisable to suspend treatment for 4 days, whilst an anti-histamine drug is exhibited. Hawking (1952) treated 50 onchocerciasis patients in Uganda with hetrazan. The dose was 50 mgm. of di-hydrogen citrate salt 2–3 times daily. The dose was increased after the first two days till 250 mgm., thrice daily, was reached. Violent allergic reactions were produced, though microfilariae usually disappeared from the skin, reappearing directly treatment ceased. Adult worms did not appear to be much affected. When a small dose of hetrazan is given intense reaction in the corium of the skin can be demonstrated. Microfilariae show evidences of degeneration. These allergic reactions are so constant that they can be used as an additional means of diagnosis.

Combined Treatment.—Burch has shown that the combination of antrypol (suramin) and hetrazan gives the best results in a series of 82 patients. Phenergan tablets control the allergic symptoms and cortisone is very useful.

Antrypol is given intravenously in a course of 8 injections at the rate of 1 grm. weekly. Hetrazan was simultaneously administered in doses of 0.25–2 mgm. per kg. three times daily for 8–6 weeks. Disappearance

of microfilariæ from the skin was astonishingly rapid after either drug. After a year's interval only 15 per cent. of the hetrazan series were free from microfilariæ, whereas 87 per cent. of the antrypol series were free. There is therefore some evidence that intravenous injections of antrypol kills off the adult worms.

Antrypol for intravenous use is used as a 10 per cent. solution, starting with 0.5 gm. and gradually increasing to 1 gm. weekly.

Recent work has confirmed the value of this combination. Ikejiani (1955) in Nigeria treated 22 cases with hetrazan, in larger doses (6 mgm. per kgm.) daily for 28 days and with antrypol intravenously, 1 gm. weekly for 10 doses. To avoid unpleasant reactions, a test dose of 0.2 gm. was given 24 hours before the first full dose. The ambulant patients had systemic reactions, sometimes with enlargement of the inguinal glands. When observed in a follow-up during the next 1½ years only 2 had mild recurrences. Conran and Waddy (1956) gave these doses for 5 weeks and found that this treatment reduces the blindness resulting from onchocerciasis and could be administered to patients in the bush.

Antrypol alone.—Budden (1956) gave this to 70 patients. Each received a total of 160 mgm. per kgm. A high proportion of adult worms died during treatment and the number of microfilariæ in the anterior segment of the eye, in the skin and in the vicinity of the nodules was greatly reduced. With this there was associated improvement in the related symptoms and signs which continued for six months. The allergic reactions due to destruction of microfilariæ is less intense than with hetrazan. Toxic reactions are transient. Albuminuria occurred in a large number and hepatitis in a few. Chartres (1955) and his wife were both cured with suramin (antrypol) after failure with diethylcarbamazine.

Other methods include systematic excision of nodules, as in Mexico, but it is not applicable to Africans.

Prophylaxis (Lebrun, Wanson, Garnham).—In the Congo rapids just below Leopoldville conditions are ideal for simulium larvæ which live on the stalks of *Pennisetum nodosiflorum*. The cycle from egg to adult lasts nine days. Then the new insects emerge at dawn and, during the next 24 hours mating and the first blood meal of the female takes place. After four days eggs are laid. Under good conditions, the female may pass through two or three gonotrophic cycles. When it feeds on a carrier of onchocerca the larval forms become infective in six days. From these facts it can be concluded that the zones of reproduction can be treated with insecticide, while the zones of dispersion require less attention. Infected flies never fly for more than 12 km. from their place of origin.

The campaign of aerial spray undertaken in 1948 sufficed to break the transmission. The Congo Rapids are too large to deal with and the Congo itself too big for larvicides to be effective, but with smaller volumes of water DDT in a concentration of 2–5 mgm. per c.m. of water and Gammexane in a concentration of 8 mgm. per litre were effective in destroying the larvæ. Therefore the only possible procedure was to destroy the adults near the river near Leopoldville, by aerial spraying, while the young adults were emerging at dawn. The spray had a residual

effect which continued to be lethal for two days. In October, 1948, a campaign of 26 daily flights was made to spray the rapids. After the first two days the city was practically free from simulium, by the fourth day villages for 35 km. around were free, and by the 21st breeding places were negative. Since that time Leopoldville has been practically free from simulium and all local transmission has ceased.

Complete eradication has been accomplished in the Koderia valley, Kenya, where Garnham poured DDT emulsion into streams infested with *Simulium neavei*. In the third case Buckley eradicated this simulium by discriminative bush-clearing of all undergrowth and small trees from the banks of two fly-infested rivers. Other campaigns have been undertaken by adding larvicides to water at Jinja on the Nile (*S. damnosum*) and in the Kakamega forest (*S. neavei*) with fair success. Fish are not killed and crab are unharmed. *S. neavei* was absent for seven years after DDT treatment of rivers in Koderia, when it was given in 0.5 parts per million at intervals of 14 days in three months.

In French Equatorial Africa spraying by helicopter has been inaugurated.

IV. DRACONTIASIS

Synonym.—Guinea-worm.

Geographical distribution.—This important parasite, *Dracunculus medinensis*, is found in certain parts of Africa and India, and appears to have been imported from America. In Africa it occurs in the Valley of the Nile, Lake Chad, Bornu, and West Africa; it has been observed in Uganda, but not in the Congo basin. It is also found in Persia, Turkestan, Arabia, and in a very limited part of Brazil (Feira de Santa Anna). Formerly it was supposed to be endemic in Curaçao, Demerara, and Surinam. *Dracunculus* is not equally diffused throughout this extensive area; it tends to special prevalence in limited districts, in some of which it is excessively common. In parts of the Deccan, for example, at certain seasons of the year nearly half the population is affected; and in places on the West Coast of Africa (Ghana) nearly every negro has one or more specimens about him. In Europe, guinea-worm is seen only in natives of, or in recent visitors from, the endemic areas. In North America, according to Chitwood, it has been found in the silver fox (*Vulpes fulva*), the racoon (*Procyon lotor*), and the mink (*Putorius vison*), but never in man. In Asia and Africa the parasite is widespread amongst carnivora. In some parts of Ghana this parasite has now disappeared owing to drying up of wells by drought.

Ætiology. *The parasite.*—The male worm has only rarely been found (see p. 1020). The female measures about 32.5 cm. to 1 m. 20 cm. in length, by 1.5 mm. in diameter. The embryos are somewhat flattened, with a tapering tail, and measure 0.5–0.75 mm. in length by 0.017 mm. in breadth.

Life-history.—The embryos of *D. medinensis* are shed into water and, swimming about actively, enter the body-cavity of a fresh-water crustacean, *Cyclops quadricornis*, or allied species, in which they develop until a length of 1 mm. is attained. (For details, see Appendix, p. 1021.)

Mode of infection.—The metamorphosis of *D. medinensis* in cyclops was discovered by Fedchenko in Turkestan and subsequently confirmed by Manson in England; but, owing to the colder climate of this country, the metamorphosis

takes longer to complete—eight or nine weeks, instead of five weeks as in Turkestan. Cyclops, containing the larvæ of the guinea-worm, are swallowed by man in drinking-water, digested, and the parasite, being then set free, works its way into the tissues of its new and definitive host.

Later, Leiper showed that when an infected cyclops is transferred to a 2·0 per cent. solution of hydrochloric acid it is immediately killed, but the larvæ, so far from being destroyed, are aroused to great activity, and eventually escape into the fluid, in which they swim freely. From this he conjectured that under natural conditions man becomes infected through the ingestion of cyclops containing these worms, the gastric juice acting on cyclops and larva in the same way as the hydrochloric acid in his experiment. In order to prove this, he fed a monkey on bananas concealing cyclops which had been infected for five weeks, and which contained fully-developed larvæ. Six months later, when the monkey died, five worms were found in its connective tissues, all possessing the anatomical characteristics of *D. medinensis*.

The evidence is now fairly complete that the life-span of the female dracunculus, before she appears on the surface of the body, extends to about one year. It is not to be supposed that every species of cyclops is an effective intermediary; if this were the case, guinea-worm infection would have a much wider geographical range.

Pathology and symptoms.—The parasite, on attaining maturity, makes for the legs and feet; these are the parts of the human body most likely, in tropical countries, to come in contact with puddles of water, the medium in which cyclops—the intermediary host—lives. The water, carriers in India are very subject to guinea-worm, which, in their case, appears on the back—that is, the part of the body against which the water-skin lies when being carried. It seems that the mature guinea-worm, by instinct, seeks out that part of the body most in contact with water.

Occasionally, the guinea-worm fails to pierce the integument of her host; sometimes she dies before arriving at maturity. In either case she may give rise to abscess; or she may become cretified, and in this condition may be felt, years afterwards, as a hard convoluted cord under the skin, or be discovered on dissection.

The haunt of the female guinea-worm is the connective tissue of the limbs and trunk. When mature, she proceeds to bore her way through this tissue, travelling downwards. In 85 per cent. of cases she presents in some part of the lower extremities; occasionally in the scrotum or on the dorsum (Fig. 218) or sole of the foot; rarely in the arms; exceptionally in other parts of the body, or even in the head. In a proportion of cases the appearance of the worm at the surface of the body is preceded by slight fever and urticaria; the onset of the skin eruption is generally at night, before the blister or other localizing signs are noted. Arrived at her destination, the female worm pierces the derma. In consequence of some irritating secretion, a small blister, containing, as a rule, numerous embryos, forms and elevates the epidermis over the site of the hole in the derma. The irritation due to this act causes a burning sensation and induces the patient to immerse his foot in water. By and by the blister ruptures, disclosing a small superficial erosion $\frac{1}{4}$ – $\frac{1}{2}$ in. in diameter. At the centre of the erosion, which sometimes quickly heals

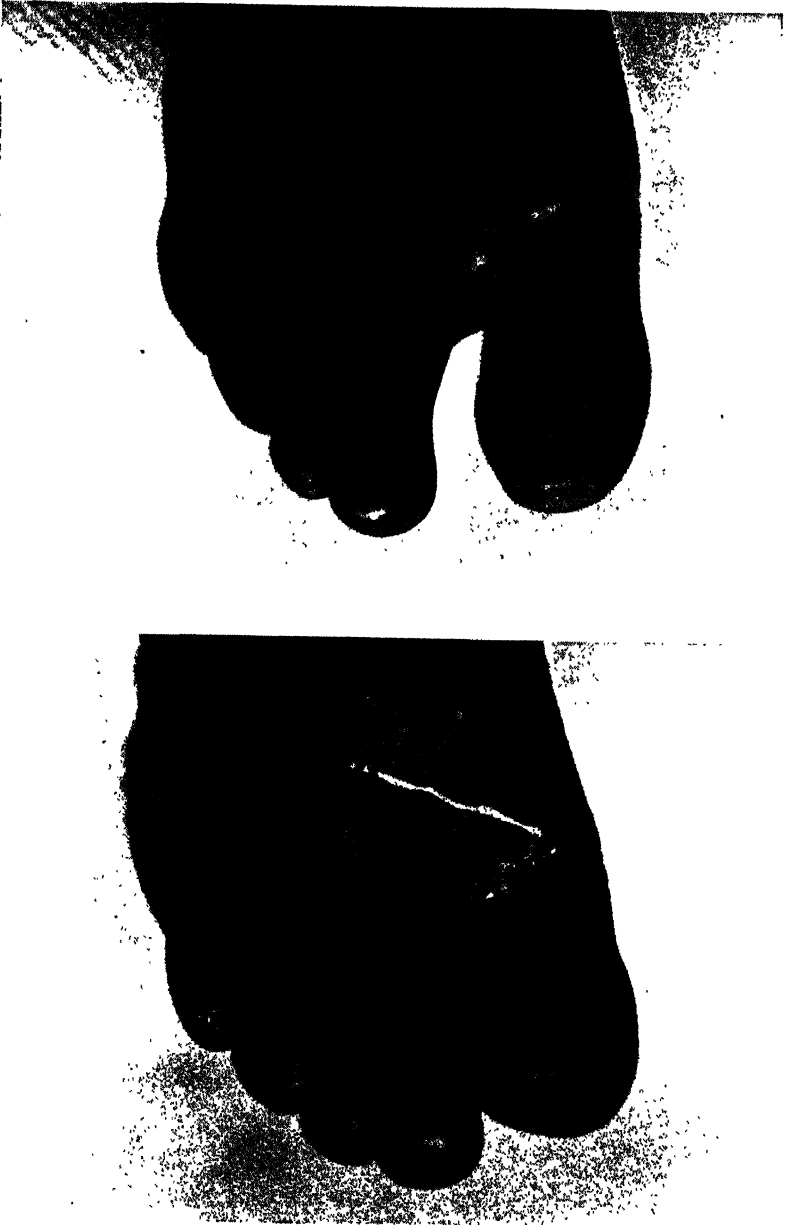


Fig. 218.—Guinea-worm disease. A. primary blister produced by head of female prior to emergence. B. Female guinea-worm protruding from interdigital cleft, showing terminal expansion containing myriads of embryos. (*P.H.M.-B. orig. case.*)

spontaneously, a minute hole, large enough to admit an ordinary probe, is visible. Occasionally, when the blister ruptures, the head of the worm is seen protruding from this hole; as a rule, however, at first the worm does not show. If the neighbourhood of the ulcer is douched with a stream of cold water from a sponge, in a few seconds a droplet of fluid—at first clear, later milky—wells up through the hole and flows over the surface. Sometimes, instead of this fluid, a small, beautifully pellucid tube, the uterus, about 1 mm. in diameter, is projected through the hole in response to the stimulus of the cold water. Apparently in this act the tissues of the head are exploded in order that the uterus may escape (Fig. 219).

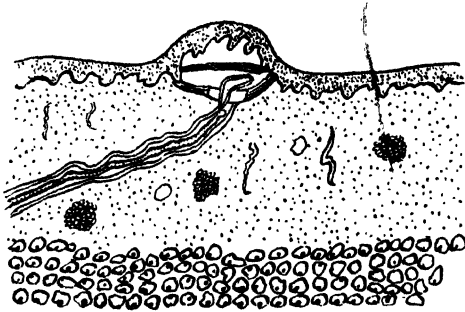


Fig. 219.—Diagram of vesicle caused by guinea-worm, showing prolapse of the uterus in the act of discharging embryos into the blister cavity.

(After N. H. Fairley and Glen Liston.)

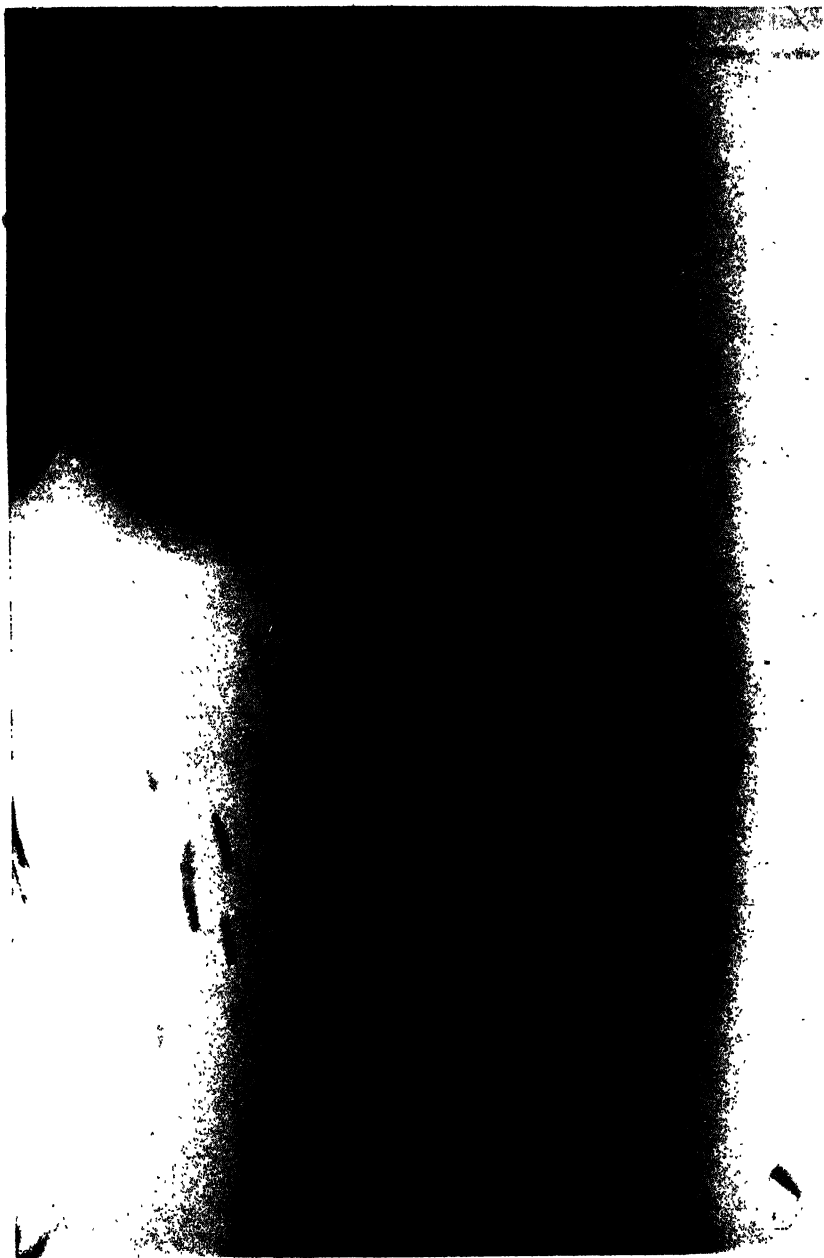


Fig. 220.—Embryos of *D. medinensis*. (Microphotograph by Mr. H. B. Bristow.)



Radiograph of leg showing guinea-worm injected with lipiodol.
(Dr. Botreau-Roussel.)

GUINEA-WORM



**RADIOGRAPH OF CALCIFIED CYSTICERCI IN
THE THIGH**

(Major-General W. P. MacArthur, Trans. Roy Soc. Trop. Med. and Hyg., 1934.)

PLATE XXII

When the tube has been extruded an inch or thereabouts, it suddenly fills with an opaque whitish material, ruptures, and collapses, the fluid spreading over the surface of the erosion. If a little of the fluid, either that which has welled up through the hole, or that which has escaped from the ruptured tube, be placed under the microscope, it is seen to contain myriads of dracunculus embryos lying coiled up, almost motionless, with their tails projecting in a very characteristic manner (Fig. 220). If now a drop of water be instilled below the cover-glass, the embryos unroll themselves, and, in a very short time, swim about, *more suo*, with great activity. If the douching be repeated after an hour or longer, a further supply of embryos can be obtained; and this can be continued from time to time until the worm has emptied herself. Apparently the cold applied to the skin of the host stimulates the worm to contract, and thereby force out her uterus, inch by inch, until it is completely extruded. The repeated birth of a limited number of progeny each time the skin of the host comes into contact with water is therefore a wonderful provision of nature. Aberrant forms of embryos were described by Moorthy and Sweet (p. 1021).

The first symptoms appear usually simultaneously with the beginning of the blister-formation, and consist of urticaria, nausea, vomiting, diarrhoea, asthma, giddiness and fainting and they are believed to be due to absorption of the toxin emitted by the worm to form the initial skin blister. The symptoms strongly suggest an anaphylactic reaction, and goats injected with guinea-worm extracts show similar symptoms, while injections of adrenalin bring about rapid improvement. Later symptoms result from the invasion of the ulcer by bacteria.

Should the worm become injured or lacerated while lying in the subcutaneous tissues, severe local reaction may develop. The part becomes extremely painful, inflamed and oedematous, and cellulitis may result, due to secondary downward growth of staphylococci and streptococci from the skin. Arthritis, synovitis, epididymitis, contractions of tendons, and ankylosis of joints have even been known to ensue. In some patients, generalized systemic symptoms accompany the premonitory urticaria, such as pyrexia, giddiness, dyspnoea and vomiting; and gastro-intestinal symptoms have been noted during the early stages of guinea-worm infection, associated with an increase of eosinophile cells in the blood; this is due to the absorption of a specific toxin, so that alarming symptoms may be produced in laboratory animals by intravenous injection of extracts of the adult dracunculus.

That the cellulitis associated with guinea-worm is due to the excretion of toxins by the mature parasite was shown by Fairley and Glen Liston, who failed to produce any local or general reaction by subcutaneous injection of the embryos themselves. Botreau-Roussel and Huard described a specific non-bacterial arthritis, especially of the knee-joint, associated with the presence of a guinea-worm in the vicinity.

Lester from Dar-es-Salaam reported the discovery of an entire guinea-worm coiled in a hernial sac; it was kept alive in the laboratory for twelve days after removal. According to Trewn, guinea-worms may present themselves after as long an interval as fifteen years from the time of infection. Massive infections are also reported, and as many as 56 adult worms have been counted in one person at the same time.

Diagnosis.—This is, as a rule, sufficiently obvious. In cryptic infections there is generally an eosinophilia. If the worms cannot be seen they may be felt underneath the skin. When both these methods fail, screening with X-rays has been of use; and injection of 2 ml. of 10 per cent. collargol

into the worm renders it opaque (Hudellet, 1919). Effete and calcified worms are easily demonstrated by skiagraphy. (Plate XXII.)

An *intradermal test* for diagnostic purposes was introduced by Ramsay. The antigen is obtained by adding to 100 ml. of ether 0.25 grm. of dried powdered guinea-worm, with frequent shakings at room temperature for two hours to remove the lipoids. The dried, ether-free residue is extracted with shaking for four hours, in 100 ml. of 0.85 per cent. solution of sodium chloride at 37° C. After centrifugation, it is passed through No. 6 Seitz filter, and 0.25 ml. of this is used for injection. A positive weal is 2-3 cm. in diameter, with outrunners.

Sequelæ.—Subacute sterile abscesses are occasionally seen, due to premature death of the female *D. medinensis*, with the liberation of embryos into the subcutaneous tissue. The condition is diagnosed by the deeply situated fluctuating swelling, not communicating with the exterior. In synovitis and arthritis, the exudate may be serpus or purulent. Generally, there is an associated cellulitis, the synovial membrane being involved by direct spread through the adjacent tissues. Permanent deformities and a history of prolonged illness in the recumbent position are invariably associated with sepsis. Bony ankylosis is rare. The joints mainly involved are the knee and the ankle, while the tendo Achillis and hamstrings are not infrequently contracted. Connor (1922) drew attention to cases diagnosed as chronic rheumatism, traumatic synovitis, periostitis or sciatica, where X-ray examination revealed calcified worms.

Treatment.—Formerly it was the custom, as soon as a guinea-worm showed herself, to attach the protruding part to a piece of wood and endeavour to wind her out by making a turn or two daily. Sometimes these attempts succeeded; just as often the worm snapped under the strain. The consequences of this accident were often disastrous. Myriads of young escaped from the ruptured ends into the tissues, and violent inflammation and fever, followed by abscess and sloughing, ensued; weeks, or months perhaps, elapsed before the unhappy victims of this rough surgery were able to get about. Too often, serious contractions and ankylosis from loss of tissue and inflammation, and even death from sepsis resulted.

If a guinea-worm be protected from injury, and the part she occupies frequently douched with water, her uterus will be gradually and naturally forced out inch by inch and emptied of embryos. Until this process is completed she resists extraction. When, in from fifteen to twenty days, parturition is completed, which can easily be ascertained by the douching experiment, the worm is absorbed or tends to emerge spontaneously. A little traction then may aid extrusion. Traction, however, must not be employed so long as embryos are being emitted. When located by X-rays and collargol, the worm may be dissected out (Hudellet).

The parasite may also be killed by injecting her, by means of a syringe, with solution of bichloride of mercury, 1 in 1000; after twenty-four hours, extraction is usually easily effected. If the worm has not shown herself externally, but can be felt coiled up under the skin, the coils should be injected, through several punctures, with a few drops of the same solution. Fairley and Glen Liston advocated aspiration of the blister-fluid before extraction, followed by pre-

cautions to avoid sepsis. The surface should first be painted with tincture of iodine. After a period of forty-eight hours, they advised excision of the worm if lying convoluted in a limited space; failing this, intermittent traction should be combined with massage. The subcutaneous injection of 9–10 min. of 1 in 1000 adrenalin hydrochloride immediately relieves the distressing prodromal symptoms, such as urticaria and asthma, from absorption of toxins.

To complete extraction of the worm, the operative procedure is as follows. It is applicable whether a blister has formed or not, or whether a sinus is present. The skin overlying the worm at some distance from the ulcer is infiltrated with cocaine and adrenalin (2 ml. of 1 per cent. cocaine and 1 ml. of 1 in 2000 adrenalin). An incision is made at right angles to the line of the worm through the anæsthetized tissues. The whitish fibrous sheath of the worm being exposed, the superior surface is incised longitudinally and a small strabismus hook inserted inside its interior. By these means the female *D. medinensis* is hooked out. The loop of the worm is held tightly in the fingers while intermittent traction and massage are again employed. Should it be impossible to liberate the distal end of the parasite, a second incision is made over another palpable segment of the worm, and both ends of the central loop are cut across and the intermediary portion removed. It is most important that the proximal head portion

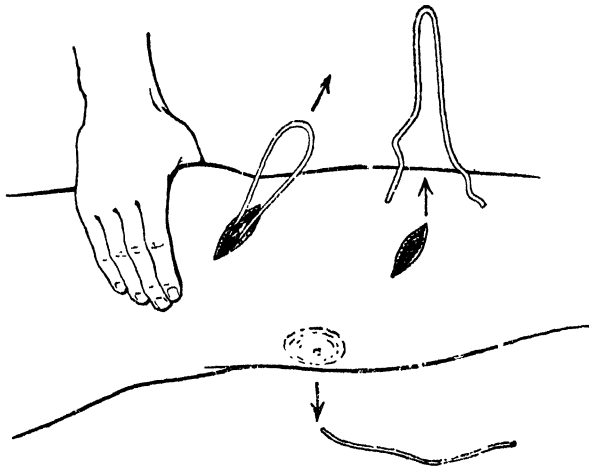


Fig. 221.—Diagram of removal of guinea-worm. (After N. H. Fairley.)

of the worm should be removed through the sinus, not drawn through the sheath in the subcutaneous tissues in the reverse direction, or otherwise there will be pollution with organisms from the mouth of the sinus (Fig. 221).

A newer treatment is by a dye, phenothiazine (Mountjoy Elliott, 1942). Finely powdered and triturated, it is emulsified with *adeps lanae* and olive oil. A certain amount of heat is required to keep the solution sufficiently fluid to be drawn up into a hypodermic needle. Each injection consists of 10 ml. of the emulsion, containing 1 gm. of phenothiazine. The site of the injection is anæsthetized by infiltration with novocaine. Three injections are usually made as near the course of the buried worm as possible. Usually, 4 gm. of phenothiazine is given in one treatment, and the site massaged for five minutes. Injections are made at weekly intervals and rarely more than two courses are needed. After 5 to 7 days the worm may be extracted by the rolling

stick method. The rolling should be preceded by strong pressure with the fingers along the course of the worm tract in the direction of the sinus. This milking action should be performed for about 2 minutes. No toxic symptoms have been noticed.

Hetrazan.—Rousset (1954) would appear to be the first to use hetrazan in treatment and prophylaxis. The best hope for success, he thinks, is during the period of larval development in the body, a period of nine months. Tablets of hetrazan of 50 mgm. were used in various dosage schemes. The highest dose was 80 tablets in five days (4 grm.). Side effects were common. Of the 31 so treated only two subsequently developed signs and symptoms. It was concluded that hetrazan exerts a marked therapeutic effect. It is best given three months after exposure to infection. In the treatment of the adult worm, when it has penetrated the skin, hetrazan should be given in maximal doses which results in reduction of the inflammatory œdema and renders the worm more amenable to extraction.

Prophylaxis.—It is evident that prevention is merely a question of protecting drinking-water from pollution by guinea-worm patients. Leiper demonstrated that cyclops are killed by raising by a few degrees the temperature of the water in which they live. He suggested heating by a portable steam generator the water in wells and water-holes which are known to be sources of guinea-worm infection. Alcock found that the addition of a trace of potash to the water is equally effective. In Mysore, Moorthy found that step-wells are the greatest source of infection, especially in high-caste Hindu houses. When barbel fish (*Barbus puckelli*, *B. ticto*, *Rasbora donicornicus*), which feed voraciously on cyclops, are introduced, the guinea-worm disappears. Otherwise the wells must be treated every fourteen days with *perchloron* (bleaching-powder substitute).

Ona Bamiro (1956) has done some useful prophylactic work with hetrazan and finds that the drug has only slight effect on the freshly-discharged embryos, but that the second-stage larvæ as well as their cyclops intermediate hosts are most susceptible to the toxic effects of this drug. In the infective stage the larvæ are killed by 20 per cent. solution in $1\frac{2}{3}$ hours. It is suggested that the drug should be used as a prophylactic by travellers passing through a guinea-worm infested area.

CHAPTER XLVI

PARASITES OF THE LUNG AND LIVER

I. PARAGONIMIASIS (ENDEMIC HÆMOPTYSIS)

Geographical distribution.—Paragonimiasis occurs in China, Japan, Korea, Formosa, the Philippines, Nigeria and the Cameroons. Seven cases were reported amongst members of the U.S. Marine Corps from the South Pacific (Samoa and Solomon Islands) during the second world war (Miller and Wilbur). In some of the endemic districts a notable percentage of the population is affected. Paragonimiasis is found in wild animals (racoons, opossum and in pigs in Georgia) in the United States, but so far no human infections have been discovered there. The spread of the disease takes place by eggs in the sputum, more usually in the fæces; this is specially the case in cats and other domestic animals.

Ætiology.—The fluke, *Paragonimus ringeri* (*westermanni*), is reddish-brown, thick and fleshy, oval, and measures 8–20 mm. by 5–9 mm. Development of the parasite proceeds in the fresh-water snail *Melania*, and thereafter the larva, or metacercaria, encysts in several species of fresh-water crabs (*Polamon* and *Parathelphusa*) and crayfish.

Man is infected by eating raw or improperly-cooked crabs, of which the Koreans are very fond, while the raw juice of crayfish is taken as a medicine for diarrhœa and whooping cough. The young parasites hatch in the ileum and in 24–42 hours penetrate the intestinal wall near the jejunum, reach the peritoneal cavity, and make their way to the diaphragm by penetrating the tendinous portion. Travelling beneath the pleura, the larvæ reach and pierce the parenchyma of the lungs, where cysts are found. In other organs they do not reach perfect growth (see Appendix, p. 948). A new form, *Poikilorchis congolensis*, has recently been described.

Pathology.—The lungs do not at first present any unusual appearances but, on looking closely, small brown spots are thickly distributed over the entire surface of the pleura and many tumour-like swellings of a deep red colour, in which the parasites are situated, can be seen. On making a section of the lungs, a larger or smaller number of what are known as “burrows” are discovered scattered about, particularly towards the periphery. These burrows consist of areas, somewhat larger than a filbert, of infiltrated lung tissue in which can be seen a number of tunnels filled with the same material that constitutes the characteristic brown sputum, which may also contain one or two trematodes. As a rule the flukes in the cysts lie in twos, side by side. The septa between the tunnels may break down and a considerable cavity thus be produced; and as this occurs in connection with one of the bronchi, with which the tunnels always communicate, it may give the appearance of a dilated bronchus. One burrow may communicate with another. It is estimated that the number of eggs coughed up in twenty-four hours is over 18,000. Tubercle bacilli and paragonimus eggs are frequently found together.

When first discovered, it was supposed that *P. ringeri* was confined to the lungs, but it may affect the liver, peritoneum, testes, intestine, skin, muscle, and brain. It may cause intramuscular abscesses. In the brain it may form a tunnelled tumour similar to those in the lungs.

Musgrave, in his study of the pathology, pointed out that the peculiar bluish, cyst-like burrows of the parasite occur in many organs and tissues. Infiltration by the eggs produces, especially in serous membranes, little brownish-red patches sometimes visible to the naked eye. The intestinal mucosa is a common seat of infiltration, which gives rise to inflammatory reaction, ending in ulceration and the appearance of eggs in the fæces. The eggs may find their way into the spinal cord, as reported by Robertson, and produce transverse myelitis. At least 100 mature parasites have been found in a psoas abscess. The eggs have been found in large numbers in the urine in a case of pulmonary infection (Weinstein, 1953).

Symptoms.—The symptoms generally begin so insidiously that it is impossible to fix their onset with accuracy. The subjects of endemic hæmoptysis have a chronic cough

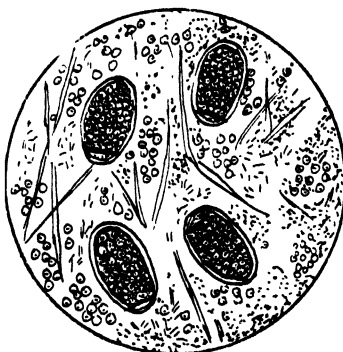


Fig. 222.—Eggs of *Paragonimus westermani* in sputum.

and a vague feeling of distress in the chest, which is usually most urgent in the morning on rising. The fits of coughing expel a peculiar rusty-brown, pneumonic-like sputum, which can be produced at will almost at any time, and often in considerable quantity. In addition, the patient is liable to irregular attacks of hæmoptysis. Though usually induced by violent exertion, such attacks occasionally come on without apparent cause. The hæmoptysis may be trifling; on the other hand, it may be so profuse as to threaten life or at least to cause intense anæmia.

Ogi stated that an outstanding physical sign in chronic cases is clubbed fingers. The physical examination of the chest is mainly negative. The patient is well-nourished. Resonance is usually normal, with a tendency to hyper-resonance, while râles can be demonstrated in a few instances.

The sputum.—Under the microscope the peculiar colour of the viscid, pneumonic-like sputum is found to be due partly to red blood-corpuscles, partly to a crowd of dark-brown, thick-shelled, operculated eggs (Fig. 222). Besides pus-corpuscles there are large numbers of eosinophil cells. Charcot-Leyden crystals are often present. The eggs vary a good deal in size and shape; they are all distinctly oval, have a yellow, smooth, double-outlined shell, and measure from 80 to 100 μ by 40 to 60 μ . If the sputum be shaken up in water, and the water be renewed from time to time, in the course of a month or six weeks—longer or shorter according to temperature—a ciliated miracidium is developed in each egg. When the mature egg is placed on a slide with slight pressure on the cover-glass,

the operculum is forced back, and the miracidium immediately emerges and begins to swim about and gyrate in the water.

Abdominal symptoms in some cases may also be present; they consist of dull abdominal pains and occasional diarrhoea. The abdominal wall feels hard and is tender; at the same time symptoms of liver cirrhosis, appendicitis, enlargement of the prostate, epididymitis and adenitis may be present.

Cerebral symptoms.—When the disease affects the brain, especially in children, a peculiar form of Jacksonian epilepsy may be a feature for a considerable period, and may end in hemiplegia, aphasia, visual disturbances, homonymous hemianopia, pareses or monoplegias of various degrees.

Generalized.—In what is known as generalized paragonimiasis, in addition to the symptoms noted above, there is generalized lymphadenitis, especially affecting the axillary and inguinal groups, often associated with cutaneous ulcerations.

Diagnosis.—Diagnosis is at once established by the discovery of the characteristic eggs in the almost equally characteristic sputum. The sputum is sticky, not foamy, and resembles that of pneumonia. Charcot-Leyden crystals are usually present. Râles and other physical signs of lung consolidation are not usually discoverable. If the intestine or liver is implicated, eggs may appear in the stools.

One-sided convulsions or hemiplegic affections in a native of, or a visitor from, the countries in which this trematode is endemic, should suggest examination of the sputum on the chance of discovering the parasite. Should eggs be found, there is a strong presumption that the cerebral trouble arises from a trematode tumour in the brain. Komiya and Yokogawa (1953) have found the AMS iii technique the most useful for demonstration of the eggs in fæces and sputa. AMS technique is a modification of the Telemann, HCl and ether methods. HCl is mixed with equal parts of sodium sulphate, 2 grm. of fæces are used and washed three times in it. Then it is centrifuged in a solution of HCl, sodium sulphate and triton NE ether.

In the endemic zones of paragonimiasis, even in the absence of eggs in the sputum, Musgrave recommended that this parasite should be suspected in cases of chronic epididymitis, enlargement of the lymph-glands or prostate, liver cirrhosis, and skin ulceration. As some of these conditions are also found in *Schistosoma japonicum* infection, the operculated eggs of paragonimus should be carefully distinguished from those of this parasite. The sputum should be examined bacteriologically to exclude the tubercle bacillus. Blood examination usually discloses a moderate leucocytosis of about 15,000 and there is usually no rise in the eosinophil cells.

The cutaneous ulcerations have to be distinguished from those of oriental sore.

Wang and Hsieh described well-defined opacities and isolated infiltrations in various parts of the lung field. American radiologists have described appearances at the base of the right lung simulating early bronchiectasis. By the method of tomography Kershaw and Ross have described more precise appearances. In the antero-posterior and lateral

aspects they find opacities made up of about six contiguous cavities. The fibrous walls are clearly outlined and there is little surrounding pneumonitis. Ch'ien and Mu-han (1955) in an analysis of X-ray findings have laid down that, in order to obtain the best skiagram of *Paragonimus* cysts, they should be as near as possible to the film. If they are in the posterior part an antero-posterior picture is best, but when in mediastinum an oblique picture is necessary. By these methods they postulated four stages in the development of the *Paragonimus* cyst: (1) a diffuse area of exudative pneumonitis around the ovum; (2) a fibrous capsule surrounding the adult parasite—the cyst stage; (3) death of the parasite, and fibrous changes penetrate the cyst, forming a fibrous nodule; (4) calcification occurs. The corresponding X-ray pictures of these stages are diffuse patches of density; isolated nodular shadows, containing vacuoles; isolated denser shadows, 7–8 mm.; very dense shadows, 2 to 5 mm. in diameter.

Ando first employed a complement-fixation test, using an extract of the body of the adult worm as antigen. This has been improved by utilizing specimens obtained from laboratory-infected cats. The tests were performed by Chung (1955) by the Kolmer-Wassermann test "half volume" technique with controls. This was positive in all 13 cases and in the C.S.F. in all those with cerebral involvement.

Intradermal tests with a 1 in 250 solution are helpful. A positive result is indicated by an immediate weal, 1–4 cm. with pseudopodia; subsequently there is surrounding erythema and intense itching. Hunter, Ritchie and others (1958) use saline extract of adult-flukes, preserved with merthiolate. Of this 0.01 ml. is injected intradermally. Out of 113 passing eggs 95.6 gave a positive reaction. From the clinical aspect paragonimiasis has to be distinguished from bronchiectasis more than any other condition.

Treatment.—So far no means of expelling the parasite from the lungs has been discovered. In cerebral paragonimiasis it might be possible by operation to remove the parasite and associated tumour, and thus afford a chance of recovery in a condition which has hitherto proved fatal. Kobayashi and Ando reported encouraging results with emetine, which is said to lessen the sexual activity of the trematodes. The drug is injected intramuscularly in doses of 1.25 ml. of a 2 per cent. solution four times daily for five days, but it must be used with great caution, especially where there is any myocardial trouble. Others have combined emetine injections with sulphadiazine, 0.5 gm. four times daily, for 10 days.

Chung (1954), in Peking, has recorded encouraging results with chloroquine therapy in three cases. For children the dose is 0.125 gm. thrice daily, over a period of two months. For an adult the dose is 0.25 gm. twice daily for two months. The total amount being 32.5 gm. There was a great improvement in the clinical condition and diminution in the number of ova in the sputum.

Prophylaxis in this, as in so many other animal-parasite diseases, lies principally in securing a pure water supply for drinking and bathing purposes, and avoiding all uncooked articles of diet, especially crabs and

crayfish, which might be supposed to contain the young parasites. The sputum and faeces should be destroyed. In Chosen, Korea, an enlightened Government has waged a campaign against crabs, and has rendered their sale unlawful, while the populace is being educated about the dangers by means of posters and advertisements.

II. CLONORCHIASIS

Geographical distribution.—The trematode responsible for this disease has been found in many Eastern countries, including India, Mauritius, Japan, Korea, Formosa, China, and the Red River Delta of Tonquin. In South China, Faust and Khaw determined that the fish-raising industry is responsible for the high incidence in Kwantung Province. In Central Japan, according to Katsurada, there are certain districts in which it affects from 56 to 67 per cent. of the population, and Léger found the eggs in 50 per cent. of the natives of the East Coast of Indo-China. A potentially endemic area has been discovered on the Pacific Coast of California, the infection having been imported by Chinese immigrants and also in Indians and in native Hawaiians from eating salted or pickled fresh water fish from China. But the disease has not spread, in the absence of suitable intermediary hosts.

Ætiology.—The parasite, *Clonorchis sinensis*, measures 10 to 20 mm. by 2 to 5 mm.; it is oblong, narrow, flat, and somewhat pointed anteriorly, reddish, and nearly transparent. Development outside the human body takes place in two different intermediary hosts—primarily, a mollusc, *Bithynia*, usually *B. striatula*; and secondarily, several species of freshwater fish of the carp family. (For further details, see Appendix, p. 943.)

Pathology.—*C. sinensis* inhabits the bile-ducts. It thickens the walls of the biliary canals and expands them in places into cavities and diverticula as large as filberts, the walls of which are thickened with fibrous tissue. In these cavities vast numbers of parasites may be found. The diverticula communicate with the bile-ducts, along which the eggs of the parasites, and sometimes the parasites themselves, escape into the intestine. The affected liver is enlarged as a whole, although the tissue in the immediate neighbourhood of the diseased bile-ducts is atrophied. The spleen, also, may be hypertrophied and the intestine in a condition of chronic catarrh. This trematode is sometimes found in the pancreatic ducts, in the duodenum, and in the stomach, associated with ascites, and even with anasarca. According to Hoepli it may produce carcinomatous changes, while Kown and his associates found new growths in the liver connected with this infection.

This parasite, which for long was supposed to be practically innocuous, is now held to be the cause of a serious cirrhosis of the liver, which may terminate fatally; indeed, there can be no doubt of this in view of the fact that several thousand parasites were present in some cases. Sambuc and Baujean counted 21,000 at one autopsy, and reckoned the total weight of the parasites at 300 grm. With this degree of hepatic involvement it is surprising that all the liver function tests are within normal limits. Plasma proteins are, as a rule, low.

Symptoms.—When the infection is severe the liver becomes enlarged, and chronic diarrhœa, with recurring attacks of jaundice, sets in. Late anasarca appears, and gradually a cachexia, resembling that of sheep-rot, is established, which, in the course of several years, may prove fatal. In

lighter infections there is indigestion, epigastric distress and, sometimes, night-blindness (Bercovitz). The Editor investigated one case in which clonorchis infection appeared to be the inciting cause of acute cholecystitis (strawberry gall-bladder).

An outbreak of clonorchiasis in displaced Europeans in Shanghai was described by Koenigstein, the origin being ascribed to pickled freshwater fish. The clinical picture was one of acute infection, with fever, enlargement of liver and eosinophilia. Eggs appeared in the faeces within four weeks, when the clinical symptoms slowly subsided.

Diagnosis.—It would be well to bear in mind this and other parasites in approaching the diagnosis of obscure hepatic disease associated with diarrhoea and jaundice in patients from the East. The discovery of the eggs (Fig. 223) in the stools should give correct diagnosis. Associated

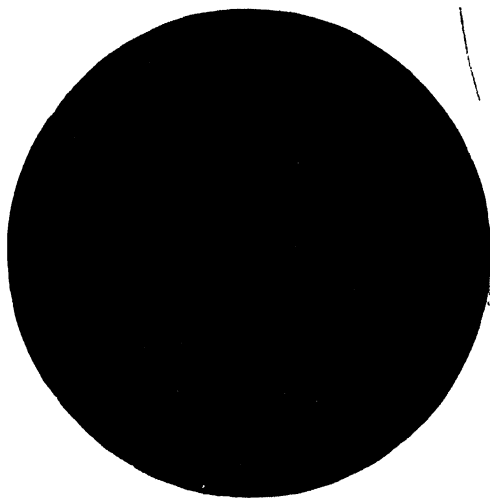


Fig. 223.—Eggs of *Clonorchis sinensis* in faeces. $\times 250$.
(Microphotograph by Dr. John Bell.)

with this disease there is generally a leucocytosis of over 30,000 and eosinophilia of over 40 per cent. Toullec and Riou employed the duodenal sound, finding large numbers of eggs in the aspirated bile, even when they failed to demonstrate them in the stools. A complement-fixation test is employed with an antigen made from a saline extract of *Clonorchis* and is fairly satisfactory.

The intradermal test (Chung, 1955) is much more reliable. The antigen is a 1 : 250 saline extract of the fluke, of which 0.1 ml. is injected intradermally and readings made after 15 minutes and 24 hours. Hunter, Ritchie and others (1958), however, find this test not so satisfactory giving 64.7 per cent. positives out of 186 individuals and false positives occur with *Schistosoma mansoni* antigens.

Sadun (1959) has improved the test by the use of a purified antigen made from rabbits experimentally infected 2 months earlier. The adult

worms, after repeated washings, were frozen and lyophilized. C.M. (fat-free antigen) gave the most reliable results and the intradermal test reached its peak 15 mins. after injection.

Treatment.—The patient should be removed to a non-infected area and given nourishing food. Intravenous emetine has been found of little avail. Several observers (Haeck, Kinugasa and others) injected foudadin intravenously with some degree of success. Chloroquine, in massive doses, averaging 10.4 mgm. per kg. for 39 days, is giving encouraging results. Thus Chung (1955) and colleagues gave chloroquine to nine patients, eight of whom completed the course; in each the ova disappeared from the stools and from the aspirated bile and in the ninth their number was much reduced. One patient relapsed two months later. The average dose of chloroquine *base* was 10.4 mgm. per kgm. body weight for as long as 39 days. The total amount given varied from 19.5–39.0 gm. The amount necessary to eliminate ova from the stools varied from 12.75–21.5 gm., and from the bile 16 to 39 gm.

Continuous non-surgical bile drainage has been extensively practised in Korea by means of the duodenal tube. It is found necessary to cocaineize the throat to prevent reflex vomiting. As a rule, it is possible to allow the tube to remain in position continuously for several days. During the day-time bile is collected every two hours, following stimulation by 50 per cent. magnesium sulphate through the tube. The bile is examined microscopically for clonorchis eggs, and the number per 4 cu.mm. counted. It is however, necessary to state that this procedure does not remove all the eggs, but it is useful in getting rid of toxic material, and the results are most spectacular when the liver is enlarged and tense.

Prophylaxis.—Manifestly, the Chinese habit of eating raw fish should be deprecated. The addition of vinegar does not kill off the clonorchis cysts. Animals and men harbouring the parasite should be prevented from fouling water, whether used for drinking, bathing, or agricultural purposes. The freshwater snails which serve as intermediary hosts inhabit the ponds in which edible fish are cultivated by the Chinese. These could be easily cleared out by energetic public health measures.

CHAPTER XLVII

INTESTINAL PARASITES

I. ASCARIASIS

Definition.—Infection of the alimentary tract with the round worm *Ascaris lumbricoides* is known as Ascariasis (for a description and life-history see p. 979).

Symptoms.—The normal situation of ascaris in the bowel is the jejunum. There, as can be shown by skiagraphy, the worms lie motionless, curled up in bundles, so that the bowel can be stuffed with worms like a well-filled sausage. Toxic symptoms are probably attributable to *ascarosin*, a mixture of albumoses and peptones. The allergic phenomena of ascaris infestation are well known. Some manifest a peculiar sensibility to their emanations, and entry to the laboratory where these worms are being dissected is enough to cause conjunctivitis, urticaria, asthma, and even "fever." The skin of these people is extraordinarily sensitive to minimal doses of ascaris substance, and in a few minutes a red and extremely sensitive wheal is produced. The passage of a worm is attended by an intolerable itching at the anus and vomiting may cause oedema of the glottis. In children, ascaris infestation may produce pallor of the face, with blue rings under the eyes and sometimes interference with nutrition;



Fig. 224.—Impacted mass of *Ascarides* in small intestine causing fatal intestinal obstruction. (*Atlas of Path. Anatomy. Cioni and Palazzi, Milan.*)

on the other hand, the infestation may never be suspected, until eggs are found in the stools.

In many instances the ascaris gives rise to no very noticeable symptoms; in others it is credited with a number of ill-defined gastric and, perhaps, nervous troubles—capricious appetite, foul breath, restless sleep, peevishness, vague abdominal pains, nausea, and so forth. It may cause most pronounced urticaria. Sometimes the worms get into the stomach and are vomited, giving rise to no inconsiderable alarm. They may even creep up the cesophagus into the mouth, or out by the nostrils, and cause suffocation by wandering into the rima glottidis. When aggregated into masses in the intestines they may cause volvulus, or even intestinal obstruction (Fig. 224). Severe lesions of the intestinal wall have been observed where macerated worms have been found in the lumen. They have been known to enter the pancreatic and bile ducts, giving rise to jaundice and abscess of the liver; to cause acute hæmorrhage pancreatitis by blocking the duct, especially in cases where the papilla of Vater has been damaged by chronic inflammation; to penetrate the intestinal wall and escape into the peritoneum, causing peritonitis (in one Chinese quoted by Hsi, over 1,500 ascaris were removed from the peritoneal cavity); or to burrow into the abdominal walls and cause localized abscess. Eggs have been demonstrated in pearl-like nodules encysted in the peritoneum and mesentery. The worms may invade the lumen of the appendix, which may be packed with eggs, and cause appendicitis. In women, they may invade the generative tract, and have been found encysted in the Fallopian tubes. In children there is characteristically a protuberant abdomen; normal digestion is disturbed; there is loss of appetite and sometimes insomnia. The most common complaint is intermittent intestinal colic. In children in Colombo, Fernando has described several acute types as follows: (a) toxic or cerebral, simulating encephalitis or meningitis; (b) acute abdominal, mimicking appendicitis; (c) respiratory, with sudden onset, dyspnoea and pyrexia. Larvæ may determine the onset of convulsions and epilepsy in children. They have been found in the thalamus of a child dead of poliomyelitis and also in the meninges (Botman, 1951). Chemical and cellular changes of the cerebrospinal fluid are associated with ascaris infestation.

Although "ascaris pneumonia" is not often diagnosed it has often been suspected in West Indian negroes. In experimental animals heavily infected with ascaris larvæ, death takes place from pneumonia after four to five days. The larvæ, in their wanderings through the lung capillaries, give rise to considerable disturbances and cause intrapulmonary hæmorrhages. In North America pneumonia is much feared by some breeders of pigs, as the ascaris of the pig is very similar to, and has the same life-history as *Ascaris lumbricoides*, this is a definite biological species, as it cannot develop to maturity in man.

Koino, a Japanese investigator, swallowed 2,000 ripe human ascaris eggs. Six days later he was attacked by definite pneumonia with dyspnoea, cyanosis, eosinophilia and pyrexia of 104° F. which lasted seven days. The syndrome of tropical eosinophilia seemed to be simulated (see p. 686). The sputum was profuse from the eleventh to sixteenth days, and contained ascaris larvæ, of which 202 were counted. The liver was enlarged; there was congestion of the conjunctiva, and severe muscular spasms. After a period of fifty days from the time of

infection, 667 ascaris, varying in length from 3-8 cm., were voided. It is said that during their migrations in the lung the larval worms may give rise to hæmoptysis. Thus Ebert (1954) has reported pulmonary eosinophilosis with X-ray signs of infiltration in a family of three who had eaten strawberries. Ascaris eggs were present in the faeces six weeks later. Beaver and Danaraj (1958) have found much the same in an adult Indian who died in *status asthmaticus*. The lungs showed eosinophilic infiltration and in sections fourth stage larvæ of *Ascaris lumbricoides* in the bronchioles. Small areas of necrosis with eosinophile cells were demonstrated in the liver.

It is estimated that each female ascaris in the bowel produces 2,000 eggs for every gramme of faeces.

Diagnosis.—It is well, when puzzled over some obscure dyspeptic condition in tropical patients, to bear the ascaris in mind. The stools must be examined with the microscope. Various concentration methods may be employed for demonstrating them (*see p. 1102*).

Ascaris infestation is usually associated with eosinophilia, but this is by no means so reliable as was formerly considered, and the Editor has seen heavy infestations without any increase of these cells. During the invasion stage, when the larvæ are resident in the lungs, there is a very definite eosinophilia, but this diminishes as the worms enter the intestinal canal. In America, Jeller, Kaspari and Leathes found in European children an average eosinophilia of 9·9 per cent. and in negro children about 5·3 per cent.

Skiagraphy can be employed in diagnosis. Films taken four to six hours after an opaque meal display ascaris as a cylindrical filling defect, or as a string-like shadow produced by opaque substance which the worm has swallowed. As a rule, the worms are arranged parallel to one another in bundles. (Plate XXIII.)

TREATMENT

Piperazines.—(a) Piperazine citrate, hydrate, adipate and phosphate are equally efficient *in vitro* in inducing a state of narcosis in the worms. Both the citrate and phosphate, being soluble in gastric contents, undergo absorption before they can reach the intestinal parasites. The sparingly insoluble adipate, by contrast, becomes coated with more insoluble adipic acid and is therefore much less absorbed. This lower degree of absorption explains the complete freedom of the adipate from the neurotoxic effects of the soluble piperazine compounds (Hartley, 1955).

(b) *Piperazine citrate* (Antepar). Goodwin and Standen found large numbers of ascaris in children in Tanganyika. Adults were given 3 grm. and children 2·5 grm. 200 immature worms were produced by a child aged 2. White (1954) gave piperazine hydrate in syrup to children (168 mgm. per kgm. per day), 0·5 grm. twice daily (68 mgm. per kgm.) for 10 days and 34 worms were passed. Faecal concentration 15 days after treatment showed no ascaris eggs. Neither starvation nor purging are necessary.

(c) *Piperazine adipate* (Entacyl) is just as efficacious as the citrate against ascaris. It is given in tablet form. The adult dose is two tablets (300 mgm.) three times daily for seven days. The consensus of opinion on these new treatments is that they are well tolerated and have no side effects, but that they are slow in action. Single worms are passed at irregular intervals, but long courses are necessary before clearance is effected.



ASCARIS LUMBRICOIDES

Radiographic appearances of *Ascaris lumbricoides* in the small intestine. Barium meal after evacuation. Note worms of various stages. The barium is retained in the intestine of the worm thus giving it a linear appearance. (Dr. T. V. Crichtlow.)

Hetrazan citrate (diethylcarbamazine).—This is undoubtedly a very effective ascaricide, but is not always well tolerated.

It must be taken 1-1½ hours after food; otherwise it is liable to cause nausea and sickness. Loughlin claims that 91-94 per cent. of worms were removed in bundles of as many as 226. Tablets are given in doses of 6 mgm. per kgm. three times daily for five days. Syrup of hetrazan is best for children in doses of 13 mgm. per kgm. on the first day and so on, or single dose of 13 mgm. per kgm. for four days.

Oil of chenopodium may be given in a mixture with liquid paraffin (one ounce) or in capsules. The maximum adult dose is 24 minims (1.421 ml.), and is usually given in two portions of 12 minims each within a quarter of an hour. Capsules of oil of chenopodium usually contain three minims each of the drug. Eight of these should be given early in the morning, in two portions of four capsules each. Jeliffe (1950) warns that this drug may cause fatal liver damage in African children. Castor oil is contraindicated.

Tetrachlorethylene is given as for ancylostomiasis, with the same precautions (see p. 796). It is given alone, in capsules, in syrup, or with liquid paraffin in doses of one drachm for an adult and proportionately less for children. It should be preceded the night before and followed by a dose of salts such as half an ounce of magnesium sulphate.

Combined treatment, oil of chenopodium together with tetrachlorethylene, is efficacious. They may be given together in a mixture, as in ancylostomiasis, but it is probably best to give the tetrachlorethylene on one day, and the oil of chenopodium on the following. The worms, when expelled, are always dead and sometimes disintegrated. It is important to warn the patient that they may not appear in the dejecta for two, or even three days, after completion of the treatment. Fatalities from carbon tetrachloride treatment, as formerly prescribed, in ascariasis have been reported, probably due to blockage of the bowel or of the bile-ducts by masses of dead worms.

Dithiazanine (Telmid), Eli, Lilly & Co., in tablets, 300 mgm. twice daily, or 200 mgm. three times daily to adults for five days, usually eliminates the worms which are stunned and are coloured greenish-blue. Faeces are also stained

ALCOPAR (B.W.).—*Bephenium hydroxynaphthoale*, 3 grm. for adults and 2 grm. for children has been proved recently to be a potent ascaricide.

Prophylaxis.—The prophylaxis of ascariasis is essentially one of efficient sanitation, and the same principles apply as in ancylostomiasis. Vegetables grown by native gardeners who use night soil as manure form an important source of infection. The pit latrine is the most valuable method of night soil disposal, and it has been found that the ascaris eggs are all killed in six months. *Eimeran*, a coal-tar preparation containing organically combined sulphur, has been found effective in killing off ascaris eggs, and is useful for latrines in the tropics (Gonturski, 1942. *Forschungs-dienst*). Ascaris prevalence constitutes the most sensitive measure of efficient sanitation. Only, when 100 per cent. of the population use latrines regularly, can any appreciable effect on the amount of ascaris infestation be observed.

TRICHIURIASIS

Trichuris trichiura, the whipworm (see p. 995), is a very common intestinal infestation in the tropics and is a constant cause of eosinophilia, sometimes as high as 30 per cent. Although generally asymptomatic, Craig and Faust express the view that exceptionally heavy infections may simulate ancylostomiasis. The most important signs are diarrhoea, blood-streaked stools, weakness, pallor, emaciation, anæmia and abdominal distension. Getz has examined such subjects by sigmoidoscopy and finds the whole wall of the lower descending colon and sigmoid covered with a coat of living worms. Jung and Jelffe (1952) consider that the clinical picture is closely related to the number of worms present in the bowel. Pain and discomfort referred to the right lower quadrant of the abdomen is constant. Hyperinfection with these worms eventually results in rectal prolapse when the worms may be actually seen attached to the prolapsed bowel. It is estimated that a worm load of 1,000 worms produce 100 eggs per 2 mgm. of faeces.

Treatment is best effected with piperazine adipate (*Entacyl*). Oral administration is best. Children up to six should get one tablet per year of life per day. Children over six and adults two tablets three times daily for seven days. Piperazine adipate is more successful than the hydrate. It has been proved that 90 per cent. are ova-free 2½ weeks after treatment with *entacyl* compound compared with 18 per cent. following the use of the hydrate.

Dithiazanine, or *Telmid* (Eli, Lilly) in tablets of 200 mgm. three times daily for five days cures 97 per cent. of adults. Large numbers of worms are passed, in one child as many as 3,162. They are stained greenish-blue and so are the ova.

Paine, Lower and Cooper (1959) report that anthelmintic effects of cyanines is due to interference with oxygen uptake and carbohydrate metabolism. Whipworms do not appear in the stools of patients till the third day. Eighty per cent. of positive cases become negative after one course of treatment (1960).

II. ANCYLOSTOMIASIS

Synonyms.—Uncinariasis; Hookworm Disease; Egyptian Chlorosis.

Definition.—A disease in its more pronounced forms characterized by great anæmia, debility, and cardiac incompetence, due to blood destruction by *Ancylostoma duodenale* and *Necator americanus*, nematodes which inhabit the small intestine, and may be present in enormous numbers.

Geographical distribution.—The ancylostome has been found so widely diffused that it may be said to occur in all tropical and subtropical countries. It occurs in Belgium, and was found by Haldane, sixty years ago, to be the cause of an epidemic of severe anæmia in a Cornish mine. In northern countries it is rare; but it is abundantly present in the south of Europe, and in the tropical and subtropical regions of Asia and America. It is especially prevalent in Egypt, Siam, South China, and Malaya. In India, Ceylon, and the East Indies it is a source of grave disability in plantations, mines, etc. It occurs abundantly on most of the Pacific islands, and exists in North and South Queensland.

Ætiology (Fig. 225).—The normal habitat of *A. duodenale* is the small intestine of man, and particularly the jejunum; less so the duodenum, rarely the ileum or lower reaches of the alimentary canal; very occasionally, it is found in the stomach. In these situations it attaches itself by means of its powerful buccal armature to the mucous membrane, from the blood of which it obtains a plentiful supply of nourishment. It is supposed to shift its hold from time

to time, the abandoned bite continuing to ooze blood for a short period. It is said to be very prodigal of the blood it imbibes, the red corpuscles passing through its alimentary canal unchanged, and the plasma alone being utilized.

The male and female ancylostomes—present generally in the proportion of one of the former to three of the latter—do not differ so much in size as do many of the other nematodes. The male (Fig. 225. *a*) measures 8–11 mm. by 0·4–0·5 mm.; the female (Fig. 225. *b*) 10–13 mm. by 0·6 mm.

Necator americanus closely resembles *A. duodenale*, but is shorter and more slender (see Appendix, p. 983). At first it was thought to be confined to the American continent, but it has been found by Looss and others in pygmies from Central Africa, and by others again in Rhodesia, India, Ceylon, Fiji, the Philippines, and elsewhere. Near Darjeeling in India it is found as a pure infestation (Lane), whilst in Egypt *A. duodenale* occurs alone.

The life history of these two parasites is identical.



Fig. 225.—*Ancylostoma duodenale*.

Nat. size. (*Dubini*.)

a, Male; *b*, female.

Reproduction and mode of infection.—The female ancylostomes produce a prodigious and never-ending stream of eggs, which pass out in the fæces. In the body of the host the development of the embryo within the egg does not advance very far; but on leaving the human host it proceeds, in suitable circumstances, so rapidly in the egg that in one or two days a rhabditiform embryo is hatched. This minute organism is very active, voraciously devouring what organic matter it can find and, for a week, grows rapidly and moults twice. After the second moulting it passes into a torpid condition, in which it ceases to eat, and growth is suspended. In this state it may live for weeks or months, moving about more or less languidly in mud, or in damp earth, but it is rapidly killed by drying. It is said that it may also enter drops of dew on blades of grass. Cort and others demonstrated that the larvæ lose their sheaths while living in the soil, and continue to exist unsheathed. Arrived in its final host, after moulting again at the end of five weeks, it acquires sexual characters and the permanent adult form.

Infestation is aided by indiscriminate defæcation, moist loamy soil, adequate shade and bare feet. There is special danger in badly-used or badly-constructed latrines and infected soils in plantations and gardens.

Looss demonstrated that the larvæ reach the intestinal canal by boring their way through the skin. From the subcutaneous tissue they enter the blood-vessels and lymphatics, and by this channel are passively transferred to the lungs. Here they leave the capillaries, enter the air-vesicles, and thence along the bronchi and trachea pass into the œsophagus, and so to the stomach.

The duration of the life of *A. duodenale* in the intestine has not been determined; some state it in months, others in years (Sonsino)—one to three or even seven. On account of liability to reinfestation, this point—an important one in prognosis—is difficult to determine.

The exact number of ancylostomes necessary to produce symptoms has exercised much attention. Some consider that 100 are necessary to produce pathogenic effects and that 500 to 1,000 worms must be present for at least six months to produce well-marked hookworm disease. Others believe that very few ancylostomes, ten or so, may affect the general health and working powers.

According to Lane, the egg-laying capacity of a single female ancylostome is about 30 eggs per ml. content of *faeces per diem*. Sweet, as the result of his studies in Ceylon, concluded that the average Sinhalese has an intensity rate of hookworm infestation of 2,200 eggs per grm. "basis-formed *faeces*," or as representing approximately one hundred ancylostomes. It is estimated that 53 per cent. of people have what is recognized as "hookworm disease," the remainder being merely carriers of worms.

Pathology.—The exact rôle of the ancylostome worm in the production of anæmia is by no means settled. The following theories have been put forward of the causation of anæmia :

- (a) Chronic loss of blood.
- (b) Absorption of specific toxin.
- (c) External conditions, such as diet and general hygiene.
- (d) The damaged gut may play a rôle through repeatedly renewed bacterial infection.

On the whole, evidence points to the dietetic factor as playing the chief part in the reaction of the human body to this infestation. As already mentioned, the bodies of the victims of ancylostomiasis are not wasted ; on the contrary, there is plenty of fat in the usual situations. The appearance of plumpness is further increased by a greater or lesser amount of general œdema. There may be effusions in one or more of the serous cavities. All the organs are anæmic. The heart is dilated and flabby, its muscular tissue being in a state of pronounced fatty degeneration. The liver also is fatty, and so are the kidneys.

If the post-mortem examination be made within an hour or two of death, the ancylostomes, in numbers ranging from a few dozens up to many hundreds, will be found still attached by their mouths to the mucous surfaces of the lower part of the duodenum, of the jejunum, and perhaps of the upper part of the ileum ; but if the examination has been delayed for some hours the parasites will have loosed their hold, and are then found lying in the mucus coating the inner surface of the bowel. Many small extravasations of blood—some fresh, others of long standing—are seen in the mucous membrane, a minute wound in the centre of each extravasation representing the point at which a parasite had been attached. Sometimes, blood-filled cavities, as large as filberts, are found in the mucosa, each cavity enclosing one or two worms and, probably, communicating by means of a small hole with the interior of the intestine. Old extravasations are indicated by punctiform pigmentation. Occasionally, streaks or large clots of blood are found in the lumen of the bowel. The hookworms inject toxins from their oral glands and secrete some anti-coagulant substance. The actual sucking of blood is a most important factor, added to the fact that the worms frequently move from spot to spot. The iron-grey colour of the worms is due to the deposition of hæmosiderin granules in their intestine; sometimes they are red from freshly imbibed blood.

In acute cases and in invasive stages eosinophilia is high, but gradually diminishes. Achlorhydria is comparatively common. In the chronic form of the disease the Van den Bergh reaction is negative. The average red cell count

is 2,900,000 per c.mm., and the hæmoglobin 37 per cent. (Haldane). The average diameter of the red cells is $7.44\ \mu$ with reticulocytes less than 1 per cent. The hæmoglobin deficiency is not really as gross as suggested, because there is considerable increase in blood volume and the reduction in total hæmoglobin is much less than that suggested by the percentage figure. The average total blood-volume is 79.5 ml. per kg. body-weight (normal 85 ml.); the average plasma volume in ancylostome anæmia is 62.6 ml. per kg. (normal 50 ml.), so that the diminution of the total blood-volume can be accounted for entirely by the diminution of the red blood-corpuscles. The blood-picture is therefore that of a secondary microcytic anæmia, which is to a great extent curable by iron therapy.

Microscopical examination of the liver and kidneys shows the presence, within the cells of the parenchyma, of grains of yellow pigment having the reactions of hæmosiderin. The bone marrow is hyperplastic : erythropoiesis being dominant.

Symptoms.—There may be dozens of ancylostomes in the intestine without any appreciable anæmia, or, indeed, symptoms of any description whatsoever. Grave symptoms are the exception. It is important, therefore, to avoid concluding that the ancylostome is the cause of every pathological condition with which it may chance to concur.

On the other hand, many inhabitants of tropical and subtropical countries are in a state of chronic starvation. Living on coarse, bulky, innutritious food, they are liable to dilatation of the stomach and dyspeptic troubles. Any additional cause of malnutrition, such as a swarm of ancylostomes and a daily, though perhaps small, loss of blood, may be sufficient to turn the scale against them. In those countries, as elsewhere, there are many who live just on the borderland between health and disease ; to such the ancylostome may prove "the last straw that breaks the camel's back." The practitioner must bear in mind that this parasite, if permitted to remain in the intestine for any length of time, may be the cause not only of remediable anæmia, but of irremediable anæmia-produced degenerations of various organs. On this account, also, its early recognition becomes a matter of the first importance. It has been pointed out by many observers that ancylostomiasis is the source of considerable surgical risk, not only in rendering the operative procedure more difficult, but also in retarding convalescence. Whenever possible, anthelmintic treatment should be instituted before operation, especially laparotomy.

Further, ancylostomiasis is an important disease from the standpoint of the employer of native labour. The invaliding and inefficiency which it causes among coolies, not to mention the deaths, are often a serious financial matter to the planter and the mineowner.

The essential symptoms of ancylostomiasis are those of a progressive anæmia—an anæmia which is generally associated with dyspeptic trouble, but which, in uncomplicated cases, is not associated with wasting. If the progress of a case be unchecked, serous effusions and fatty degeneration of the heart ensue, and death may occur from syncope or from intercurrent complication. Œdema may be localized, or there may be general anasarca. Most commonly it is confined to the face or legs.

Ground itch or ancylostome dermatitis is usually the first symptom noted (*see* p. 800), but one of the earlier is pain or uneasiness in the epigastrium. This is generally increased by pressure, but for the time

may be relieved by food. In some people it may produce an acute and ever-present epigastric pain, which closely resembles duodenal ulcer and may often be mistaken for it. The appetite, sometimes defective, is more often ravenous, though its gratification is apt to give rise to dyspeptic trouble of various kinds—to colic, to borborygmi, and perhaps to diarrhoea of imperfectly digested food. Constipation may be present in some instances, irregularity of the bowels in others. The taste may be perverted, some patients exhibiting and persistently gratifying an unnatural craving for such things as earth, mud, or lime—what is called *pica* or *geophagy*. The stools sometimes, though rarely, have a reddish-brown tinge from admixture of half-digested blood and sometimes they may contain small flakes of blood-tinged mucus. Pure blood is seldom passed; and an extensive hæmorrhage is rare, although, *post mortem*, quantities may be found in the small intestine. In the quiescent period the occult blood test is positive. Fever of an irregular intermitting, or even a sub-continued type is common. On the other hand, the temperature may be constantly subnormal, or these conditions may alternate. After a longer or shorter time, symptoms of profound anæmia gradually disclose themselves. The mucous surfaces and the skin become pallid, the face is puffy, and the feet and ankles are swollen. All the subjective symptoms of a definite anæmia now become more and more apparent; there are lassitude, breathlessness, palpitations, tinnitus, vertigo, dimness of vision, mental apathy, depression and liability to syncope. The circulation is irritable, and hæmic bruits can be heard over the heart and larger blood-vessels. Ophthalmoscopic examination may reveal retinal hæmorrhages.

Some of these symptoms, were it not that with the advancing anæmia there is no loss of weight, might suggest the possibility of tuberculous or cancerous disease or Bright's disease. Though hæmocytometric estimates testify to a slow and steady fall in the blood corpuscles until the lowest limit compatible with life is reached, there is no true poikilocytosis as in idiopathic pernicious anæmia, no excessive leucocytosis as in leukæmia, and not necessarily any enlargement of lymphatic glands, liver, or spleen. There is generally a marked eosinophilia of about 7-14 per cent., though in rapidly fatal cases these cells tend to disappear. The depression in the hæmoglobin value (M.H.C.) of the corpuscles is considerably greater than the fall in their number.

The rate of progress is very different in different cases. In some, a high degree of anæmia, and even death, may result within a few weeks or months of the appearance of the first symptoms. Such rapid cases are rare; more frequently the disease is exceedingly chronic, ebbing and flowing, or slowly progressing, through a long series of years. Acute cases develop terminal diarrhoea with passage of much mucus and, occasionally, blood, and are apt to be mistaken for various forms of dysentery.

Should such serious ancylostomiasis occur before puberty, the growth and development are apt to be delayed and stunted (Fig. 226).

It is not surprising that the severe nutritional changes associated with ancylostomiasis affect the mental powers of an afflicted population. Prolonged exposure in the European has led to the production of a race

known as the "mean white," stunted both in mental and in physical capacity. In Jamaica, in districts where the whole population suffers from ancylostomiasis, not only are the people intensely indolent, but they are also predisposed, on this account it is said, to larceny and other crimes.

The practitioner in the tropics should always be on the look-out for subacute infestations in Europeans on plantations and in mines. This does not apply solely to the men, but to their wives and children as well. Minor degrees of anæmia, an undue tendency to fatigue, lassitude and digestive disturbances are to be ascribed to this infestation, even where, from the habits of the patients, it might not be suspected. In Europeans undoubtedly the infestation may take place *via* the mouth and alimentary tract, but European children who are apt to play in sand, often used as a site for defæcation by natives, become infested in the usual way, *via* the skin.

Ancylostomiasis and pregnancy.

—It is found that hookworm disease exerts a deleterious influence on pregnancy, and that in heavily infested districts it is the most common cause of repeated abortions and miscarriage. Moreover, a heavy maternal and foetal mortality is associated with it, and early interruptions of pregnancy and neonatal deaths are also included among its effects; it is estimated that the combined foetal and infantile mortality from this cause is almost 60 per cent. In the absence of skilled treatment, the chances of a successful pregnancy are remote, if the hæmoglobin percentage has fallen below 60 at the commencement. Women who are heavily infested show a predisposition to toxæmias, such as pre-eclampsia and nephritic toxæmia.

Diagnosis.—Provided it is suspected, ancylostomiasis is easily diagnosed. In tropical countries, in patients coming from tropical countries, and in miners who work in very warm mines in cooler climates, anæmia with concurrent eosinophilia should always suggest a microscopical examination of the fæces (*see* Appendix, p. 1100). The dyspeptic symptoms may simulate those of duodenal ulcer and it has been noted that



Fig. 226.—Ancylostomiasis in a South American Indian boy, showing stunted growth, characteristic facies, and protuberant abdomen. (By permission of the Rockefeller Foundation.)

sometimes free acidity shows a higher rise than that usually observed and that high levels may be maintained in spite of varying degrees of severe anæmia. If the eggs of *A. duodenale* or of *N. americanus* are discovered, and no other reason for the anæmia is made out, the presumption is that one or the other of these parasites is responsible; at all events, no harm is likely to result from treatment based on this supposition.

The presence of occult blood and the digestive disturbances may mislead the uninitiated. Cases are known to have been subjected to partial gastrectomy for duodenal ulcer and the correct diagnosis has only been made at a later date.

On the other hand, if no eggs are found, it must not be concluded that the case is not one of ancylostomiasis; for sometimes, in the later stages of the disease, symptoms will persist although the parasites which caused them in the first instance have disappeared spontaneously, or have been got rid of by treatment. The usual method of diagnosis by microscopic examination of simple smears of stools does not convey a quantitative idea of the severity of the infestation. The grade runs from one to a thousand or more worms. Fæcal diagnosis has been rendered more accurate by the method of Clayton Lane, known as the flotation concentration method (see pp. 1101, 1103), and by other techniques. In the majority of cases a test for occult blood in the fæces is positive, and Charcot-Leyden crystals are frequently found.

Unfortunately X-ray examinations by barium meal are disappointing. The worms are not outlined by the opaque material, neither do they ingest the barium, as does ascaris, and so render themselves identifiable. In Ross Golden's "*Roengen Ray Examination of the Digestive Tract*," 1949, the appearance in the jejunum is illustrated and descriptions of the changes in the intestinal pattern, such as coarsening of the mucosal folds by Krause and Crilley, Hodes and Keefer, are to be found in Nelson's *Loose-Leaf Diagnostic Roentgenology*, 1955.

TREATMENT

I. Oil of chenopodium (*Chenopodium anthelminticum* = goose-foot, wormseed, "Jerusalem Oak") has a sharp, burning, nauseating taste, and is put up in hard gelatin capsules. For routine the dose is 1.5 ml. (24 min.) in capsules containing 3 minims (0.177 ml.) each. Eight of these capsules should be given—in two lots of four capsules at an interval of half an hour. For children, the dose should be 1 min. for each year of age up to 16, three hours after a light meal. A quarter of an hour after it a strong saline purge (sodii sulph. $\frac{1}{2}$ oz.) is given, with the object not only of washing the unabsorbed portion of the drug out of the intestine, but also of expelling the partially paralysed worms.

II. Tetrachlorethylene (C_2Cl_4) is soluble to the extent of 1 part in 10,000 of water. It is preferred to carbon tetrachloride by many, as having a pleasanter taste and being equally potent and much safer. It has been given by Soper to adults in doses of 1.6 ml. combined with 0.8 ml. of oil of chenopodium. Maplestone gave 4 ml. to men under 140 lbs. in weight. It may be given without excipient and may be mixed directly with a purgative, such as sodium sulphate. The dose for children is 2 ml. As a general rule it is dispensed in the same way as carbon tetrachloride and is subject to the same precautions.

III. Combined treatment.—It is generally admitted that combined treatment with tetrachlorethylene and oil of chenopodium is more

efficacious than the use of either drug alone. The two mix readily. The dose recommended is 2 ml. (min. 84) of tetrachlorethylene with 1 ml. (min. 17) of oil of chenopodium made up to 28.42 ml. (one fluid ounce) in liquid paraffin. The same precautions being taken, it may be given in one dose or in two halves. Tetrachlorethylene and oil of chenopodium treatment can also be given on two consecutive days. Sodium sulphate, $\frac{1}{2}$ oz. in a tumblerful of water, should be taken one hour afterwards.

The following is a practical and easily tolerated method of administering both drugs:

- (1) Starve overnight.
- (2) 8.30 A.M. : 2 capsules (gelatin) of oil of chenopodium of 7.5 mins. each.
- (3) 8.45 A.M. : tetrachlorethylene, 40 mins. (Four capsules of 10 mins. each.).
- (4) 9.0 A.M. : mag. sulph. 4 drachms in water. Stools should become liquid within four to sixteen hours. If not, mag. sulph. must be repeated.

Ancylostome eggs may be passed in the faeces for six days after effective treatment. If they persist beyond this period, the course should be repeated.

It is hardly possible to get native patients into hospital for treatment, so that systems of treatment to be completed at one sitting may have to be devised, e.g., the anthelmintic may be followed in half an hour or so by a dose of salts.

IV. Carbon tetrachloride (CCl_4 —*tetrachlormethane, tetraform*), a drug closely allied to chloroform, was originally introduced by Hall as a vermifuge and has been found suitable for the mass treatment of ancylostomiasis, but has now to a great extent been superseded by tetrachlorethylene.

The dose for an adult is 1 dr. (3.5 ml.) taken in hard gelatin-coated capsules, each containing 30 min. (1.776 ml.) of carbon tetrachloride, after a partial fast of eighteen hours without preliminary purgation. A saline purge (sodii sulph., $\frac{1}{2}$ oz.) is necessary 15–20 minutes after the drug, and an enema of hot water is usually required to empty the bowel. The treatment is best commenced at 8 a.m. and one-half of the total dose is taken after a quarter of an hour interval.

V. Hexylresorcinol, 1 : 3 *dihydroxy-4-hexylbenzol*, is a white, waxy, crystalline substance, sparingly soluble in water, but exceedingly so in alcohol or vegetable oils.

Give a light evening meal consisting of soft foods only, and the following morning give the dose *on an empty stomach*. The dosage for adults and children over twelve years of age is 5 pills, hard gelatin capsules or crystoids; for children over eight to twelve years, 4 pills; six to eight years, 3 pills; under six years, 2 pills, 0.2 grm. (3 gr.) each, with a glass of water. No food of any kind should be taken for at least four hours after treatment. Water may be taken freely, but alcohol is definitely contra-indicated. The patient may go about his usual occupation immediately after treatment and eat what he likes at the end of four or five hours. A saline purge should be given twenty-four hours after treatment to remove the dead worms. The patient may continue to pass worms for as long as ten days or two weeks after this single dose. If instructions as to food are carefully followed, one dose is usually sufficient.

Re-treatment is sometimes necessary because of re-infestation, or because the patient has not followed instructions about food. Treatment should only be repeated after two weeks, if eggs are still present in the faeces.

In cystoids the crystalline hexylresorcinol is gelatin-covered. If the gelatin covering becomes broken the drug may cause irritation and burning pain to oral and oesophageal tissues. To avoid this, the cystoids *must be swallowed whole* with a glass of water; under no circumstances must the patient crush or chew them.

VI. Bephenium hydroxynaphthoate (*Alcopar*).—Goodwin, Jayewardene and Standen (1958) have introduced this new treatment of ancylostomiasis which promises well especially against *Necator americanus*. It is remarkably non-toxic and there are no side-effects. A single dose for an adult of 2-3 grm. is remarkably effective (reduction of egg count of 100-75 per cent.) in 69 per cent. of patients. 8 grm. alone, or preceded by a purge, may be combined with piperazine citrate syrup and is, apparently, more effective. It is as good, but probably not better, than tetrachlorethylene. For children, especially when marasmic and anæmic, whose precarious state precludes the use of tetrachlorethylene, the dose is 2 grm. daily for 4 days.

Convalescence.—The dieting of convalescents from serious ancylostome disease must, for a time, be very carefully conducted. A rich, full dietary is to be avoided until the powers of digestion have become re-established; otherwise, enteritis and diarrhoea may prove very troublesome and retard recovery. The anæmia responds to large doses of iron—ferrous sulphate—in doses of 24-36 gr. daily for three weeks, or even longer. Azmy and Zanaty recommend small blood transfusions, 200-300 ml., which induce an increase of polymorphonuclear leucocytes and red blood corpuscles.

In cases of severe anæmia it may be wise to give a preliminary course of iron, with a generous and balanced diet, before administering the anthelmintic; in these cases full doses of tetrachlorethylene should be given with caution; it may be better to give a dose well below the toxic level and to repeat it as the patient becomes stronger. McFadzean and Wong (1953) insist that, in Chinese patients with extreme anæmia, it is better to treat the blood condition first, leaving the worms for the present *in situ*. Intravenous saccharated oxide, at a concentration of 20 mgm. iron per ml. (*Ferrivenin*), was given in doses of 50 mgm. on the first day, 100 mgm. on the second and 200 on the third and subsequent days. The œdema disappeared, enlarged cardiac shadows became normal, cardiac murmurs disappeared and previously palpable livers became impalpable. By the mouth they gave 1.5 grm. ferrous sulphate with 150 mgm. of ascorbic acid in divided doses daily.

Assessing results of treatment.—Under ideal circumstances all stools passed after treatment should be collected, diluted with warm water, vigorously broken up and stirred, then filtered through a fine-meshed sieve (25 meshes to the inch). The defunct or stupified worms may be picked out with forceps from the sediment. This process is facilitated by transferring it to a black photographic tray. A soft brush is used to scatter the particles. On account of their grey colour they are difficult to discern, but their recognition becomes easy with practice.

When the examination is made shortly after the stool has been passed a proportion of the worms will be found still alive and exhibiting their peculiar sinuous movements. In native cases sometimes 100-400 worms

or more can be recovered, but in Europeans a total of 70-100 is considered an exceptional figure.

The necators can be distinguished from ancylostomes macroscopically by their fine, curved heads.

Prophylaxis.—Fæcal contamination of the soil and water must be prevented and promiscuous deposition of fæces about huts, villages, and fields must be interdicted. Tea, coffee, cocoa, banana, rubber and citrus plantations, by reason of the intensive cultivation required, are potent sources of infestation. Abundant and easily accessible latrine accommodation must be provided in coolie lines, in miners' camps, in native villages, and along the highways of traffic. The Chinese plan of storing night-soil for months in large, cemented, water-tight pits is a good one. It is known that, if the eggs of the ancylostome are kept in pure fæces, the embryo is developed and escapes in due course; but it is also known that unless the larva be supplied with a certain amount of air and earth it soon dies. The thing to be avoided, therefore, is the mixing of *fresh* fæces with earth. Conditions of warmth, moisture and shade favour infestation, but the infective stages of ancylostome larvæ are killed in a few minutes by direct sunlight. By the Chinese system the embryos of the ancylostome larvæ are killed and, at the same time, a valuable fertilizer is secured for the agriculturist. The presence of standing water is an advantage as it dilutes the bacterial food of the larvæ and they cannot feed in water. A rise in temperature increases activity of the larvæ, which use up the food reserves, so that in the tropics they rarely survive longer than six to eight weeks.

It is manifest that, in devising privies and sanitary regulations, the habits of the people they are intended to benefit must be taken into account; if native habits and prejudices are ignored, any system, no matter how perfect it may be in theory, will fail in practice. In America, intensive mass treatment after the installation of satisfactory latrines has been found most effective. The provision of a fool-proof latrine for natives is the chief difficulty. So far the "bored-hole" latrine, 16 ins. in diameter, has proved most acceptable. This is deep enough to prevent migration of hookworm larvæ, produces no odour and does not encourage fly breeding, but it must have a concrete or pressed steel squatting plate.

Until a few years ago, efforts at the prevention of ancylostomiasis were directed towards treating the surface of the soil, but recent work has shown that the ancylostome larvæ spend a considerable part of their life in the deeper layers.

Therefore a most important factor underlying efficient prophylaxis of ancylostomiasis in a community is the life-span of the infective larva during its existence in a free state in the soil. Practical experience gained by the directing authorities in the "hookworm campaign" suggests that this is much longer than experimental evidence indicates. According to Cort, Augustine and Payne, the life of the infective larva under these conditions does not exceed six weeks, and during that time it does not wander outside a 4-in. radius in a lateral direction, but can migrate to the surface from a depth of 36 in. Baermann showed that the larvæ may be

recovered with ease from soil thought to be infective; the technique consists in placing the suspected soil in a receptacle, together with a quantity of water; the larvæ then rapidly migrate into the fluid, where they can be found and recognized.

Education of children in schools by means of diagrams and instructional films plays an important part in health propaganda in the United States. In South America it is noted that, although children wear shoes at school, where the chance of infestation is not great, they commonly run barefoot at home, where infestation is likely to be acquired.

Clayton Lane estimated that out of 315 million inhabitants of India and Pakistan, 45 million wage-earners were subjects of ancylostomiasis. Employers of labour in the Darjeeling district computed that the labourer's earning capacity, when freed from this disease, is increased by 25-50 per cent.

An energetic and many-sided campaign against the hookworm was waged in the United States, Asia, and Africa, financed by Mr. Rockefeller. State and county dispensaries for free examination and treatment of applicants were established with temporary beneficial result.

ANCYLOSTOME DERMATITIS

A form of dermatitis affecting the feet of coolies on plantations in Assam, in the West Indies, and probably elsewhere in the tropics, is ascribed to the penetration of the skin by ancylostome larvæ, and precedes by two to four months the generalized symptoms of ancylostomiasis. The disease is of much economic importance to the planter, and is variously known as ground itch, pani-ghao (Assam), water itch, water-pox, water sores, sore feet of coolies, cow itch (Queensland), sabañones (Venezuela), candelillas (Colombia), chauffie (Grenada) and mazamorra (Puerto Rico).

The soil in the neighbourhood of coolie lines is extensively contaminated by faecal matter. The bare feet of the coolies are constantly soiled with this larva-laden earth; and in this way, in many tropical plantations, Looss's experiment is unintentionally carried out on a large scale. Dermatitis, vesiculation, and may be pustulation, or even extensive ulceration, and probably ancylostomiasis anæmia, ensue. A condition resembling larva migrans (*see* p. 836) is often produced by allied species *i.e.* *Ancylostoma braziliense* and *A. caninum* of the dog. The services of the affected coolie are lost to the planter until the irritation subsides and the anæmia is cured.

Fülleborn published the most complete account of this subject (1932). He pointed out that the ancylostome larvæ can only enter the skin when the soil conditions are favourable. They cannot enter through water alone, nor can they readily bore through the hard skin of the sole of the foot; they pass less easily through the tough skin of the negro than the soft epidermis of the European. It was shown by Khalil that the presence of a suitable host has no special attraction to the larvæ, but they are attracted by warmth (*thermotaxis*). The appearance of the skin lesions is dependent upon the number of invading larvæ. As Schüffner showed, the inboring larvæ first form a red point, and soon a small blister forms in which the larvæ can be demonstrated in sections, and the irritation of the skin is noted after some twenty minutes. Probably, the entrance of the larvæ also causes opportunities for the ingress of bacteria with formation of

blebs and pustules, and this is the real "ground itch." It is by no means proven that ground itch is invariably *ancyllostome dermatitis*, for it is not found in Egypt where this disease is rife.

III. CESTODIASIS

The tapeworms, *Tænia saginata* and *T. solium* and their cystic forms are common enough in the tropics and subtropics, their distribution being regulated by the presence or absence of their appropriate intermediary hosts—the ox in the one case, the pig in the other—and by the habits of the population in cooking and conservancy.

The broad tapeworm (*Diphyllobothrium latum*) occurs in Norway, Sweden, Russia, Turkestan, Japan (where the natives eat raw fish), Lake Michigan, Madagascar, and on the shores of Lake Ngami, South Africa (see Appendix p. 967).

The treatment of this tapeworm is usually successful and responds to 4 grm. of oleoresin of aspidium followed by Epsom salts. The very severe degrees of anæmia are not usually seen in the tropics in association with this parasite. Injections of liver extracts are given in after-treatment. The reticulocyte peak is reached in eight days. *Dibothriocephalus* anæmia has recently been shown to be due to the absorption of large quantities of vitamin B₁₂ by the parasites and it is said that when liver in dry powdered form is administered orally the anæmia is rapidly cured. Björkenheim in eighteen cases of pernicious anæmia associated with *D. latum* found some presented symptoms of subacute combined degeneration of the cord.

The other cestodes of man which have any claim to be regarded as special to warm climates are *Hymenolepis nana*, *Diphyllobothrium mansonii*, and *Spirometra mansonioides*.

TREATMENT OF TAPEWORM INFESTATIONS

General statement.—Preliminary starvation appears to be necessary for one day. On this sodii sulph. $\frac{1}{2}$ oz., or castor oil $\frac{1}{2}$ oz., should be given to clear out the bowel; the food should be restricted to weak tea, toast and unlimited amounts of lemonade and glucose D.

I. Filix mas treatment.—*Extractum filicis liquidum*, dose 45–90 min. (2.66–5.33 ml.), has a disagreeable taste and is apt to cause vomiting, so the drug is best prescribed in gelatin capsules.

Capsules contain 15 min. each of the liquid extract. The dose of these is one to six, according to the age of the patient. It is effective against *Tænia saginata*, *T. solium*, and especially against *D. latum*. The most difficult species to dislodge are *T. saginata* and *Hymenolepis nana*. On the morning of the treatment the patient should have a small cup of tea. For an adult man the full dose of filix mas is $1\frac{1}{2}$ dr.; for a woman 1 dr. For specially resistant cases up to 120 minims (2 dr.) may be given with safety, as follows:—

8 a.m.: two capsules of 15 mins. of filix mas.

8.30 a.m.: repeat.

9 a.m.: repeat.

The mixture in syrup is sometimes better, as follows:—Filix mas 8 ml.; acacia 8 grm.; cinnamon water 42 ml.; glycerine 14 ml. Divided into 3 doses at 15 min. intervals.

The patient must then lie quiet and take nothing but sips of sodii bicarb solution, 120 gr. dissolved in half a tumbler of hot water with the idea of removing mucus from the small intestine. At 10.30 a.m. half an ounce of sodii sulph. should be given. The bowels being opened freely by the salts, segments of the tapeworm should soon appear. All motions should be saved and strained to search for the head; should this not be seen, a soap-and-water enema should immediately be given.

The patient must rest in bed the whole day when undergoing treatment. The Editor has had most success in detaching the head by a combination of filix mas with atebirin. On the first day (day of preparation) the patient takes 0.8 grm. in four doses of two tablets each (0.2 grm.) and 1 tablet on the second, the day of treatment, directly on waking. Atebrin has an action on the head of the worm and stains the segments yellow. The filix mas course follows as above.

Treatment with filix mas must not be repeated oftener than once a month, otherwise toxic symptoms, such as polyneuritis and paralysis of the iris (filic acid poisoning), may ensue.

Intraduodenal treatment of tapeworm.—Sawitzky recommends giving 30 grm. sod. sulph. in the afternoon, and starving the patient for the rest of the day. Next morning the bowels are opened by an enema, the patient swallows a catheter and is placed on his right side. The catheter enters the duodenum in 1–2 hours. He is then turned on his back, and a small glass funnel is attached. An emulsion of ethereal extract of male fern, 50 grm., gum arabic mucilage, 5 grm., sodium bicarbonate, 0.5 grm., distilled water, 50 ml., is prepared. About one-quarter of this amount, equivalent to 3–4 grm. (50–60 min.) male fern, is introduced; immediately 50 ml. (1½ oz.) of warm 50 per cent. solution of sodium sulphate is poured in and the catheter extracted. Expulsion takes place in two hours.

II. Atebrin, or mepacrine, without filix mas, has been recommended by several observers, notably Hockenga (1951), in doses of 0.8 grm. by the mouth followed by an aperient. Milk diet on the day before and a purge of castor oil are necessary. On the morning of treatment 0.6–0.8 grm. of atebirin are given, two tablets every five minutes with water. Two to four hours later the purge is repeated and food withheld until the bowels are opened.

Trevinov and Sandovala treated 62 patients with atebirin—54 harbouring *T. saginata* and *T. solium* and 5 had a dual infection. A feature of the scheme is the addition of 0.1 gr. phenobarbitone before the atebirin, of which 8 tablets are given at five minute intervals and with each a capsule of 0.6 grm. sodi bicarbonate. Two hours later the saline aperient is given. Seaton (1955) has improved upon this treatment by intraduodenal infiltration with atebirin, grm. 1, dissolved in 100 ml. of warm water. Sodium amytal gr. iii is given as a sedative before intubation. 15–30 minutes later 60–80 ml. of 30 per cent. sodii sulph. are infiltrated by the same route. Fabienke (1954) has reported 28 cured out of 34.

III. Azacrin, an acridine dye, allied to atebirin, has been given to 30 cases, 23 with *T. saginata* and 7 with *T. solium* by Ahunada and others (1954). Two tablets of 100 mgm. each are given to children and 700 mgm. to adults. The technique and spacing are given above.

IV. Dichlorophen (Anthiphen).—Seaton (1956) has given this drug, which is well-known as an anthelmintic in dogs. The dosage is 3–6 grm. on two successive days. The advantage is the extreme simplicity. No starvation or purging are necessary.

V. Tetrachlorethylene and oil of chenopodium.—Tetrachlorethylene anæsthetizes tapeworms and, especially when combined with oil of chenopodium, aids in their expulsion. It is combined as:—

Tetrachlorethylene . . .	3i	(3.5 ml.)
Ol. chenopodium . . .	℥xv	(0.88 ml.)
Paraff. liq.	3i	(28.42 ml.)

This should be given in two doses, as in ancylostomiasis. Adults should receive the full dose; children under six, 2 dr.; up to eight, 3 dr.; up to fourteen, 4 dr. The mixture should be made up fresh daily. Half an hour afterwards the patient should be given a saline aperient, or *Pulv. jalap. co.* 1–2 dr. (3.55–7 ml.) may be used.

Gentian violet has been used to expel *Hymenolepis nana*. Halawani has had better successes with chloroquine (aralen). This amino-quinoline is also credited with anthelmintic properties for *T. saginata*. Eight tablets or 2 gm. are said to suffice when followed by a dose of castor oil. These optimistic claims remain to be confirmed. Cusso, or Koussou, a decoction made from the flowers of *Brayera anthelmintica*, is said to be efficacious in Abyssinia for removing *T. saginata*. In Anatolia benzine has a great reputation. The preparation used is *Benzinum petrolii* (D.A.B.6). A previous evacuation is secured by an infusion of senna. The dose is 60 ml. for adults, 20 ml. for children of 2 to 5 years, 30 ml. for children of 6 to 14 years. (Wigand and Warnecke, 1952).

IV. CYSTICERCOSIS

Though the cysticercus, or bladder-worm stage of *Tænia solium*, normally develops in the pig, and infestation of man takes place by eating pork, which contains the larval *cysticerci*, yet occasionally man himself may serve as intermediate host through accidental ingestion of the eggs of *T. solium*. The embryos may migrate to almost any organ, especially the muscles of the limbs, tongue, neck, or ribs and sometimes the lungs, liver, or heart, and they have been removed from the eye and may remain viable for as long as 56 years (Lawson, 1939). One of the most striking recent contributions to medicine has been the demonstration by MacArthur that the embryos show a peculiar predilection for the brain. It has been known for some time that individual cases of cysticercosis may be accompanied by epileptic seizures. Investigations on epilepsy in young and otherwise healthy British soldiers, with good antecedents, has shown that cysticercosis is the cause. In one batch of 22 cases investigated by MacArthur, 10 were proved to suffer from cysticercosis. In another 82 cases in British soldiers, who had served in India, evidence of infestation with *Tænia solium* was obtained in 22. Indigenous cysticercosis in England has been recorded. Dixon and Hargreaves, in a study of 284 cases, found that in 89 per cent. radiographic examination of the skull was negative.

In some instances the fits commence about the time the cysts are first detected; in others there may be a quiescent period of some years between the appearance of the cysts and the first epileptic seizure, or, in other instances, the cysts may become palpable after the onset of epileptic fits. The number of palpable cysts varies widely in different cases. Large ones which have been under observation for years may vanish in a few days. The bigger cysts usually contain dead larvæ and the cyst capsule is tense, owing to the large amount of contained fluid. The death of the larva is in some way associated with an increase of this fluid.

Pathology.—In the brain the cysticercus becomes enclosed by a wall of neuroglia; small round cells and a few plasma cells are present between the delimiting neuroglia and the surrounding normal brain tissue, but later the tissues surrounding dead and disintegrating cysticerci undergo active degenerative changes with a marked cellular response. To the naked eye the degenerating



Fig. 227.—Section of cysticercus from brain. (*Carnegie Dixon and J. D. Willis, Lancet, 1941.*)

tissues may be visible around the cysticercus as a discoloured ring, and later, if the patient survives, they undergo necrosis. This dead area, which may extend 5 mm. beyond the cyst, is ringed off from the normal brain by a wall of sclerosed neuroglia. (Fig. 227.)

After a variable period, determined in part by the resistance of the host, the parasites die and often undergo calcareous change. Calcification commences in the scolex, while the cyst capsule and its contents are unaffected. Calcification may stop at this point, and the cyst-wall may collapse through the escape of the fluid, or the collapsed cyst may be flattened out by pressure of the surrounding muscles and calcify in an extended form. Apparently, three years elapse between death of the cysticercus and calcification in the tissues, but cysts in the brain take longer.

Symptoms.—The fits may resemble the Jacksonian type, with cyanosis, biting of tongue and involuntary passage of urine. In some instances they are irregular, and cerebral tumours may be suspected. Nervous symptoms other than fits may be produced; thus the initial clinical picture may be that of disseminated sclerosis or cerebral tumour. Psychical states may supervene with cerebral irritability and loss of memory. Other manifestations are disequilibrium, involuntary movements, disordered behaviour, vomiting, tinnitus and giddiness (Bickerstaff, 1955).

Usually, the invasion of cysticerci gives rise to no general reaction, but the patient notices the gradual development of small subcutaneous or intramuscular swellings. More rarely, a general toxæmia with pyrexia develops. Sometimes, too, the localized intramuscular swellings resemble a muscular dystrophy. Cysts may be present in large numbers without the patient's knowledge until they are discovered accidentally by radiological examination. In one case the

first fits commenced during treatment in hospital for *T. solium*, whilst Dixon and Hargreaves found evidence of previous tapeworm infestation in 26 per cent. There may be a history of incomplete fits, often regarded as hysterical, and every degree from petit mal to Jacksonian epilepsy. Intense headache may be the one symptom preceding a fatal attack. Psychical disturbances, melancholia, or acute mania may dominate the picture. Mental deterioration may be very insidious in onset, on the other hand left-sided hemiplegia of sudden onset has been recorded.

Apparently no prophecy can be made of the duration of the epileptic symptoms. Sometimes the seizures cease without apparent cause; in others they persist for eight years or longer. MacArthur has seen one cysticercus alive in the brain after a lapse of fifteen years. There have been several fatal cases in which the cysts have been found limited to the brain.

Diagnosis.—The most helpful sign in diagnosis is the development of palpable cysts in the tissues, and these may number from one to thirty or more. They may be the size of a hard pea, a hazel-nut, or even a pigeon's egg. Their situation varies widely; they have been found in the lips, masseter muscles, neck, chest, abdominal walls, back and groin, and if not numerous they are easily overlooked. Indeed, unless evidence of cysticercosis is systematically sought, diagnosis may be missed, as nodules may be absent at the time of examination, only to come out in crops at a later date. When these external cysts are absent, as Edwards remarks, "failure to think of cysticercosis is the greatest impediment to its diagnosis." The radiological evidence may not be convincing for some years, as calcification does not usually take place for four or five years after infestation. Whilst they are alive the body is relatively tolerant, though they become active irritants when dead and calcified.

To demonstrate cysticerci, a suitable cyst is excised under local anaesthesia and the host capsule is enucleated. The appearance of the translucent membrane with its central "milk spot" is characteristic. If alive, the parasite may evaginate the head and neck, or it may be induced to do so by immersion in hot saline.

When partially calcified, a good skiagram will show it as a small elongated shadow, but the completely calcified cyst gives a characteristic appearance (Plate XXII). In the muscles cysticerci are oat-shaped due to pressure, whilst those in the brain are circular. In showing up calcification "high penetration" is more effective than slight under-exposure. The exposure should be that ordinarily employed for bone detail. Evidence of calcification within the brain has been demonstrated. Unfortunately, in the early stages, the cysts are diaphanous and do not show up. Therefore, a negative radiograph of the skull is of no significance. The size of the cysts depends mostly on their age and situation. Eosinophilia affords no aid to diagnosis. Complement-fixation tests have proved disappointing, and a negative test does not exclude the possibility of infestation. The intradermal Casoni test is positive in about 50 per cent. of cases. Trawinski developed a precipitin test, using an antigen made from *Cysticercus cellulosæ*. There may be no changes in the cerebro-spinal fluid. De Sèze and others, however, stated that excess of lymphocytes, a positive colloidal benzoin reaction and eosinophil increase, in the absence of a positive Wassermann reaction, suggest cysticercosis. It must be remembered that the Ghedini-Weinberg complement-fixation, as well as the Casoni intradermal test, are group immunological reactions, whether hydatid extract or cysticercus fluid is used as antigen.

Treatment.—Intravenous injections of antimony tartrate have been tried, often without much effect. Although instances of successful localization

and removal of single cerebral cysticercal cysts have been recorded in the literature, usually such interference is unjustifiable. Luminal and bromides are helpful in controlling fits. Observation on tissue changes which follow the death of intracerebral cysticerci suggest that destruction of large numbers of these parasites might make matters worse.

In actual practice, temporary amelioration of symptoms, after removal of one or more cysts, has often been followed by death.

Prophylaxis.—This cannot be undertaken until the source of infestation has been ascertained. It is commonly believed that human cysticercosis is an accidental complication, auto-infection being caused by the ingestion of eggs or possibly by regurgitation of segments of *T. solium* into the stomach.

Section X.—DISEASES DUE TO POISONS, INCLUDING SNAKE-BITE, AND INFECTION WITH DIPTEROUS FLIES AND LEECHES

CHAPTER XLVIII

VEGETABLE POISONS

POISONS USED FOR CRIMINAL PURPOSES

THE inorganic poison most generally used by tropical races is arsenic in some form, cleverly intermingled, as a rule, with flour, inserted into the grains of maize or millet, or introduced into sweets, as in Egypt; in Malay, powdered croton seeds or datura are used. Natives usually possess a much wider and more intimate knowledge of organic poisons than do civilized peoples.

In Brazil, common native poisons are derived from *Paullinia pinnata*, which contains an alkaloid, *timboin*, and from the fruit of *Thevetia ahonai*, the active principle of which is *thevetosin*; both of these cause vomiting and respiratory failure.

In Indonesia a poison extracted from the roots of *Milletia sericea* produces debility, headache, diarrhoea, collapse and death.

In the Pacific islands the native poison is derived from the fruit of *Barringtonia speciosa*.

In India a large number of vegetable poisons are in use. In the Madras and Bombay Presidencies an extract is obtained from the roots of *Nerium odorum*, the white oleander, which contains two glucosides exerting a specific action on the heart. Similar substances, *urechitin* and *urechitoxin*, from *Urechites suberecta*, exert a cumulative action, and therefore sudden death may be produced without arousing suspicion of poisoning.

The juice of an *Asclepias* (or milkweed) is used in India as an infanticide; the symptoms are vomiting, salivation and cramps. The roots of various species of aconite (*Aconitum ferox*, etc.) are used for the same purpose; death takes place rapidly—in three to six hours, as a rule. Several species of Apocynaceæ, such as *Cerbera odollam* and *Thevetia nerifolia*, the sap and seeds of which contain a glucoside, *thevetin*, are very deadly, death from cardiac failure taking place in twelve to fifteen hours. In Southern India, Burma, and Ceylon a decoction of the fruit of *Gloriosa superba*, one of the Liliaceæ, allied to squill, is employed for criminal and suicidal purposes. The active principle, *superbin*, causes gastro-intestinal irritation and cardiac failure within four hours. The commonest poison in India and Ceylon is datura, one of the deadly nightshades, of which there are several species. The seeds, mixed with food or drink, produce a state of extreme mental exaltation, followed by coma; the active principles are *atropine*, *hyoscyamine*, and *scopolamine*.

In Africa the leaves of *Hyoscyamus faherlez*, containing *hyoscyamine* and *scopolamine*, as active principles, are used by Tuaregs of the Sahara. On the West Coast of Africa, a decoction of a cactus, colloquially known as "oro," produces blisters in the mouth, vomiting and gastro-intestinal irritation, collapse and death. In China, opium is the suicidal poison most frequently used, especially by women.

Curare, the potent arrow poison of S. American Indians was known to Sir Walter Raleigh in 1595. The material was obtained from the giant vines of the Amazon and Orinoco, called "bushropes" by explorers which include *Chonodendron tomentosum* which is the main source of curare. Curare poisons by causing paralysis of the muscles as shown by Claude Bernard in 1857. It has a molecular structure similar to that of acetylcholine. As a result of this molecular similarity the "receptors" in the muscle, upon which acetylcholine acts, cannot distinguish between them and in this physiological manner relaxation of the muscle is produced. It has now revolutionized anæsthesia and in a refined state is known as *d-tubocurarine chloride*. Since then synthetic forms of curare have been discovered by Biret and are being widely used.

DISEASES DUE TO THE INGESTION OF POISONOUS FOODS AND WATER

LATHYRISM AND FAVISM

This disease, characterized by various nervous manifestations, such as ataxy, spastic paraplegia, weakness and muscular pains, without psychical disturbances,



Fig. 228.—Scissors-gait due to adductor spasm in lathyrism. (McCombie and Young, 1927. *Ind. Journ. Med. Res.*, 15, 453.)

occurs in Abyssinia, Algeria and India in those districts in which vetches, "Khasari," *Lathyrus sativus*, and allied species, form the main article of diet. Howard and his colleagues (1923) demonstrated that the wild vetch (*Vicia sativa*), which contaminates this crop, is harmless, but that the poison is contained in a variety, *var. angustifolia*, which contains alkaloids: *vicine* and *divicine*. There are two varieties of *L. sativus*: the larger called *lakh* or *teova*: the smaller *lakhori* or *teovi*. Rudra (1952) considers that the toxic principle is selenium. The methionine excretion is diminished. A similar disease occurs in animals fed upon the same food. The arms and trunk are seldom involved; incontinence of urine and sexual impotence are early and common symptoms. The disease is very chronic and seldom ends fatally. The muscular atrophy produces the typical "scissors gait" (Fig. 228). Shah (1939) claimed that cases improve rapidly on dietetic and vitamin treatment, and Anderson (1939) suggested that elements of the vitamin A complex are involved and that they are effective in treatment. Rudra advises the administration of methionine.

Bhargawa (1956) found the dried seed or flour of *V. sativa* is non-toxic to pigeons, so that lathyrism may be the result of germinating or damp lathyrus seeds.

ATRIPLICISM

A combination of cutaneous and nervous symptoms in China is caused by eating leaves of *Atriplex littoralis*. The earliest symptoms consist of itching of the hands, followed by oedema, and often by bullæ; the finger-tips may become gangrenous, cutaneous hæmorrhages may occur, and the face and eyelids become cyanotic and oedematous. In many aspects it resembles Raynaud's disease and erythromelalgia. Yu Ky described a syndrome after eating the leaves of *Atriplex serrata*, or *Chenopodium hybridum*, in which the symptoms and signs are similar, and it is thought that the skin lesions can be ascribed to light-sensitive dermatosis.

ACKEE POISONING (VOMITING SICKNESS OF JAMAICA)

An acute and fatal condition, locally termed "the vomiting sickness," has been known for many years in Jamaica. It is found principally in rural districts in circumscribed epidemics. The causation and nature were neither apprehended nor understood, although several Commissions had attempted to elucidate them. To Sir Harold Scott belongs the merit of clearing up this mystery, and of indicating simple and practical methods of prevention, which have saved the lives of many children. It is estimated that since 1886 over 5,000 lives have been lost in Jamaica from this cause.

Cicely Williams (1955) has stated that this disease is not limited to the ackee, but to other herbs used for "bush teas." Recently other observers, such as Hill (1953), have raised doubts of the very existence of vomiting sickness as a separate entity. Stuart and others (1955) found extreme hypoglycæmia (blood sugar levels as low as 22 mgm. per 100 ml.) in children with this illness. They laid the foundations for its logical treatment by prompt and large doses of glucose. Biopsy and necropsy showed fatty changes in the liver with almost complete absence of glycogen. The course of the disease suggested a temporary enzyme block, inhibiting gluconeogenesis for which the name of *acute toxic hypoglycæmia* is proposed. The ackee, when studied by Hassall and Reyle (1955), was found to contain in its seeds two polypeptides—*hypoglycin A* and *B*—which produced fatal hypoglycæmia in laboratory animals. This study may be important to the fuller understanding of carbohydrate metabolism in diabetes mellitus.

Vomiting sickness is confined to the West India Islands, practically to Jamaica, and occurs principally in the cooler months, from November to April.

Symptoms.—A previously healthy child suddenly complains of abdominal discomfort, vomits several times, recovers, and perhaps falls asleep. Three or four hours later, vomiting—now of a cerebral type—returns. Within a few minutes, convulsions and coma supervene, and death follows, on an average, about twelve hours from the initial vomiting, though it may take place in one and a half hours. The case-mortality amounts to 80–90 per cent. In those who recover, convalescence is complete in twenty-four hours.

During the attack the temperature is normal or subnormal, rarely rising to 101° F.; the pulse rate is 90 to 100; the respirations are 26 to 30, sometimes, as death approaches, of Cheyne-Stokes type. The pupils are slightly dilated and, until near the end, react to light. Except during the convulsive seizures, there is no muscular rigidity. Post-mortem examination reveals hyperæmia of viscera with a tendency to minute intestinal hæmorrhages, together with marked fatty changes, especially in the liver and kidneys, and sometimes in the pancreas and heart-muscles.

Ætiology.—Scott showed, on what must be regarded as convincing evidence—clinical, seasonal, epidemiological, and experimental—that vomiting sickness is the result of poisoning by a fruit, much used by negroes in Jamaica, called *ackee*,

the fruit of *Blighia sapida* (Fig. 229), a tree very common in the island. A similar species is found on the West Coast of Africa, where it is known as *Irsin*. When mature and in good condition, this fruit is wholesome enough; if gathered, before it is quite ripe and before it has opened while on the tree, or if gathered from an injured branch, or opened after falling to the ground, it is poisonous. The poisonous element in the immature and unsound fruit appears to be soluble in water, for "pot water" in which the ackees have been cooked is much more toxic than cooked fruit. The poison is precipitated by alcohol. Jordan and Burrows showed that the toxic principle is also contained in the seeds and in the arilli of the ackee which have not yet "opened." Two polypeptides have been isolated—*hypoglycin A* & *B*.

Treatment.—An emetic, and washing out the stomach with an alcoholic fluid

during the primary vomiting, are indicated. Scott was insistent that administration of alcohol must be prompt.

Prophylaxis.—When the fruit in various stages falls to the ground, only the opened pods, that is the ripe fruit, should be used for food. The immature unopened pods should be destroyed.



Fig. 229.—Ackee fruit. *Blighia sapida*.
 $\frac{1}{4}$ nat. size. (After Byam and Archibald.)

MANIOC AND NAMI POISONING

Manihot aipi (sweet cassava) and *Manihot utilisima* (bitter cassava) are ground roots extensively used in the West Indies. From the latter are produced starch, tapioca, and cassava cakes. Poisoning arises from failure to remove the

contained glucoside and enzyme. In the presence of water these release free hydrocyanic acid, so that nausea, vomiting, distension of the abdomen and impeded respiration result.

Nami (*Dioscorea hispida*, Dennst. and *D. hirsuta*, Bl.) is a colloquial term for a species of yam, employed for food in parts of the Philippines. It has frequently caused food poisoning, and occasionally it has been put to criminal purposes. An alkaloid—*dioscorine*—has been obtained from the full-grown tubers.

CORAL PLANT (*Jatropha multifida*, L.)

Coral-plant poisoning was reported by Raymond from Tanganyika, the symptoms being colic, cramps and thirst, with subnormal temperature. Two species, *J. curcas* and *J. glandulifera*, are common in the West Indies. *J. glandulifera*, since it grows rapidly, is used in Jamaica for fencing enclosures. The nuts taste like sweet almonds, and the plants are known as "physic nuts"; a third species, *J. multifida*, is known as the "French physic nut." *J. gossypifolia*, which occurs in the West Indies, is known as the wild cassava, or "belly-ache bush," and its seeds contain an intestinal irritant like croton oil. A fifth species, *J. urens*, from the same area, bears leaves provided with stinging hairs, which cause itching, smarting, flushing of the face, swelling of the lips and faintness. Recovery is rapid after ejection of the poison by vomiting.

GINGER PARALYSIS (*Jake paralysis*)

This is a flaccid paralysis of the distal muscles of the limbs without involvement of sensory nerves. The arms are affected later. The deep reflexes, especially the knee-jerks, are exaggerated. Deaths have been recorded from respiratory paralysis in South Carolina and Tennessee from eating Jamaica ginger adulterated with triorthocresyl phosphate and in Morocco from olive oil similarly treated.

JENGHOL POISONING

Jenghol poisoning (Djenkol) occurs in Java from eating a bean, *Pithecolobium lobatum*, or *D. geminum*, and was described by de Langen, Hijman and Van Veen. The symptoms are chiefly pain in the renal region, dysuria, and often anuria. The urine frequently contains blood-casts and sharp acid crystals of jengcolic acid. The presence of these crystals in large numbers in the urethra causes necrosis, fistula and extravasation. The jenghol bean has a high vitamin-B content and is used as food in spite of its toxic properties. The beans are buried in the ground for ten days and eaten when they begin to sprout. Ingestion of these beans by normal persons is followed by an increase in excretion of sulphur.

DATURA POISONING

Various plants belonging to the order Solanaceæ are used in many parts of the tropical world to produce unconsciousness. The seeds of *Datura fastuosa* are used by Thugs in India for this purpose, but datura poisoning is by no means confined to India. The seeds have a slight taste and are consequently easily introduced into food; their intoxicating properties are widely known. *D. sanguinea* is used in Peru and Colombia, *D. ferox* and *D. arborea* in Brazil. The characteristic seeds are found in the fæces and, in fatal cases, in the small intestine.

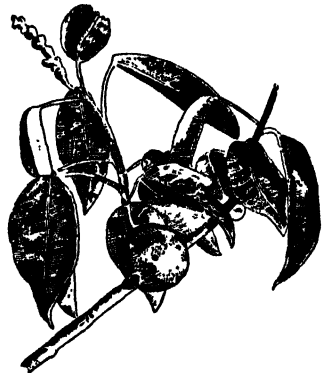


Fig. 230. *Hippomane mancinella*, fruit and inflorescence. (After K. V. Earle.)

MANCHINEEL POISONING

The manchineel, or manchineal, *Hippomane mancinella*, belonging to the order Euphorbiaciæ, is a tree thirty to fifty feet high and of a circumference of five to ten feet, distributed along the coastline of North, South and Central America and the West Indies. It is particularly common in Barbados, Grenadine Islands, and the Archipelago of Les Saintes, in French West Indies. Two varieties are recognized, one with "holly" and the other with "laurel" leaves; both are equally toxic. The first, which resembles a crab-apple, has a pleasant odour. (Fig. 230.)

The latex contains a greenish resin, which is the active toxic principle. Like the Upas tree, the manchineel has been said to bring death to those who sleep under its shade. All parts of the tree are toxic, but the amount of latex in any portion varies with the season; even the dry wood and sawdust are endowed with irritant properties. Hypersensitive people who pick manchineel apples (or fruit) may suffer from a skin eruption with erythema, bullæ and vesiculation. Toxic dermatitis is especially likely to affect the genitalia and the anus, causing a vesiculo-pustular eruption which may be confined to the corona penis. Conjunctivitis with pain, photophobia and blepharospasm may result from the

introduction of the latex into the conjunctival sac. Severe dermatitis brought about by handling dried wood-powder is thought to be allergic.

If the fruit is eaten, as it may be by ignorant visitors, children or insane people, vesiculation of the buccal mucous membrane with diarrhoea and blood-and-mucus stools may ensue. Fatal poisoning may result.

Manchineel juice on the skin should be washed off with sea-water. Blisters should be kept aseptic, and, if extensive, should be treated like a second-degree burn. When the fruit has been eaten, emesis should be induced.

ALCOHOLISM AND DRUG HABITS

Alcohol poisoning occurs in varying degrees among nearly all native races, and in symptoms and course does not differ materially from alcoholism in other parts of the world. Rum (65–72 per cent. of alcohol), obtained from the fermentation of molasses, is used in the West Indies and South America; arrack (50–60 per cent. alcohol) is manufactured in India, China, and Java from fermented rice or from palm sap; while a slightly fermented drink, toddy, is obtained from sweet sap of various palms, and is drunk in India, Ceylon, and West Africa. In South America a potent alcoholic drink is made from the fermented juice of *Agave americana*, and is known as “pulque.”

Opium poisoning.—The opium habit, either eating or smoking—the symptoms of which are too well known to require description—is common throughout the tropics. Opium poisoning is also a favourite form of suicide, especially among women.

Cannabis indica.—Indian hemp, or *hasheesh*, grows in India, Persia and Arabia, and is a variety of the common hemp, *Cannabis sativa*. The leaves are powdered down, and either chewed or smoked in a preparation known as *bhang*; an extract of the flowers is known as *ganja*. Both these preparations cause great nervous excitement and, if persistently used, often lead to permanent insanity, the main features of which are hallucinations and illusions. *Hasheesh*, in various preparations, often with the addition of extracts of various Solanaceæ, such as *datura* and *nuxvomica*, is habitually taken daily by millions of the inhabitants of Africa and Asia. The most stringent Government regulations have been framed to suppress trade in this drug.

Kawa, or yangona, the powdered root of one of the Piperaceæ, prepared to form a beverage, is drunk on festive occasions throughout Polynesia. Formerly the root was masticated by specially selected girls in the preparation of the drink, a practice which was then a prolific source of tuberculosis. Over-indulgence in kawa induces a state of hyperexcitement, with loss of power in the legs. Chronic intoxication produces debility, with coarse roughened skin.

Betel.—Chewing betel, the leaves of *Piper betel*, together with lime and areca nut (*Areca catechu*), is a common practice in India and Ceylon, and generally throughout the East. The mouth, lips and teeth are stained a bright-red colour. It produces a flushing of the face, and has mild stimulant and possibly anthelmintic properties. In Central Africa the nuts of the kola tree (*Sterculia sp.*) are chewed habitually, and act, like betel, as a stimulant, without, it is said, producing any detrimental effects.

Cocaine (*Erythroxolon cocoa*) is widely used in India and in parts of South America as a stimulant and intoxicant. The leaves, first dried in the sun, are chewed with lime or, as in India, with betel. This drug produces a loss of sensation in tongue and lips, the pulse is accelerated and there ensues a period of hilarity and exaltation. The drug addict soon becomes emaciated and cachectic.

MUSHROOM POISONING

There are many poisonous species of mushroom, particularly the genus *Amanita* in Southern Europe and U.S.A., more especially *A. phalloides*, the "death cap." These mushrooms cannot be distinguished by their taste and are said to possess an agreeable flavour. They can be recognized by persistence of a portion of the veil encircling the stem a little below the cup. *A. muscaria* contains an alkaloid, *muscarine*, which is allied to pilocarpine. Atropine constitutes an efficient antidote.

FLAX DARNEL (*Lolium linicolum* or *L. temulentum*) POISONING

Brinton (1946) has described recurrent epidemics of food poisoning in the native population of Aden due to Ethiopian wheat containing this poisonous weed, known in local Arabic as *Miscara* ("tipsy"). Each weed seed is covered by a mould known as *temuline*. Within a quarter of an hour the patient becomes dizzy, with headache, slurred speech and generalized tremors and staggering gait. Sometimes there is diarrhoea, nausea and abdominal pain. Stupor and coma supervene and last for about ten hours. This state is known as "Lolism" and is common in Ethiopia.

CATHA EDULIS OR MIRAA POISONING

Miraa is a local name (muiragi, khat, cafta) of a tree, *C. edulis*, about 20 ft. in height, indigenous to Africa. The leaves or twigs may be chewed or infused to make "Bushman's tea," or may even be smoked, when it induces a happy mellow sense of friendliness. Carothers (1945) describes cases of mental disturbance in addicts. *C. edulis* contains three alkaloids, *cathine*, *cathinine* and *cathidine*. Except that it is not an analgesic the action resembles that of cocaine.

EPIDEMIC DROPSY

Synonym.—Argemone Oil Poisoning.

Definition.—Epidemic dropsy somewhat resembles beriberi. Clinically, it is characterized by dropsy associated with cardiac symptoms, but without paralysis or anæsthesia.

History and geographical distribution.—This condition was first noted in Calcutta in 1877; it has since occurred there sporadically, but vanishes in the hot season. In Mauritius, in 1879, it affected one-tenth of the coolies, of whom a large number died. An epidemic broke out in Fiji in 1926 and was limited to Asiatics; no native Fijians were affected. In Purulia (Nagpur, India) there have been epidemics at intervals since 1913, the worst being in 1934 when over 2,000 were attacked. Meaker (1949) has described an outbreak in coloured labourers in N.W. Cape District.

Ætiology.—In spite of the apparently wide distribution of this disease, most of the information comes from India, where this form of poisoning is especially seen in the Hindus, particularly in females. Children under puberty are less liable than adults; sucklings are seldom affected. The weak and the robust are equally susceptible. It has been remarked that very few are of the poorer class, nearly all coming from the middle and upper classes.

The outbreak in Fiji in 1926 was attributed to mustard oil used in the preparation of curries, and later, Banerji and Ghosh in Bengal came to the same conclusion. The Mexican poppy, *Argemone mexicana*, is a common weed in India as well as in Australia, where it is usually mixed with wheat and fed to fowls. In them it produces changes in the comb, paralysis of legs and œdema of wattles and subcutaneous tissues reminiscent of epidemic dropsy in man. Bhattacharjee

was the first to bring forward evidence that oil from the seeds of this poppy was responsible for toxic manifestations in man. Later, Pasricha showed that the toxicity of contaminated mustard oil could be eliminated by heating to 240° C. for fifteen minutes. Lal and his colleagues found that the seeds of *A. mexicana* (*Sialkanta* in Hindu) are present in many stocks of mustard seed in India, used in the preparation of Katakari oil for cooking. Cullinan (1947) described an outbreak amongst African troops in Madagascar which appeared to be due to fungus-infected rice. *Sanguinerine* is believed to be the toxic principle of argemone oil. In animal experiment it has been found to cause capillary dilatation and interferes with oxidation of pyruvic acid.

The ætiology now appears clear. Argemone oil, under experimental conditions, produces symptoms indistinguishable from those of "epidemic dropsy." It can be detected by a simple colour test, on adding nitric acid to contaminated mustard oil. Sarkar did not consider that this is sufficiently delicate, but stated that argemone oil, when heated with ferric chloride, in the presence of strong hydrochloric acid and ethyl alcohol, gives an orange-red precipitate. Two ml. of the oil to be tested are taken in a test-tube, 2 ml. of concentrated hydrochloric acid are added, mixed and heated in a water-bath at 92-95° F. for two minutes. Then 0.8 ml. of ethyl alcohol is added, the mixture shaken thoroughly and kept in a water-bath for one minute. Two ml. of ferric chloride solution are then run in, the contents mixed thoroughly by shaking, and the whole heated in a water-bath for another 10 minutes.

Pathology.—De described as characteristic extensive vascular dilatation in the deeper layers of the skin. The heart-muscle shows no degenerative changes, but there is thinning of the muscle-walls, and muscle fibres are separated by dilated capillaries; similar changes are present in the ciliary body of the eye, leading to excess of fluid in the anterior chamber. Shanks also found capillary dilatation wherever the vessels are least supported, and this is most obvious in fatty tissues, whether subcutaneous, subpericardial or subperitoneal. Similar changes are seen in the lungs, in the cervix uteri, in the ovaries and in the intestines. The liver usually presents a "nutmeg" appearance (Shaha). In Fiji vascular outgrowths resembled sarcoids and bled profusely. The chief changes occur in the blood-vessels, which are dilated and surrounded by proliferating endothelial cells.

Chatterjee and Halder found that in an average case the total erythrocyte count is about 3.8 millions, whilst the hæmoglobin is reduced to 11 grm. per 100 ml. The lymphocyte percentage is raised and there is usually considerable eosinophilia. The reticulocytes are not increased as a rule.

Symptoms.—Dropsy is almost invariably present. It usually appears first in the legs, and in some instances is confined to them; in others it involves the entire body. Occasionally, it is very persistent, recurring during convalescence. Fever also is very constant; sometimes it precedes, sometimes it accompanies, sometimes it follows the dropsy. It is rarely high, ranging usually from 99° to 102° F. Diarrhœa and vomiting generally ushered in the disease in the Mauritius epidemic. In Calcutta these symptoms were not so frequent, although by no means rare, occurring at both earlier and later stages. The total duration is about six weeks. An outbreak in the employees of the E. Indian railway was reported by Goel in 1945. There were 476 cases. The largest proportion were œdematous and a considerable number had diarrhœa and pyrexia. Œdema of feet and legs lasted for two weeks. There was patchy pigmentation over nose, malar bones and shins. Tachycardia was common and mortality 4.4 per cent.

Peripheral neuritis is absent and the knee-jerk is not abolished, but usually distressing aching of muscles, bones and joints is prominent. An exanthem, erythematous on the face, rubeolar on the trunk and limbs, was frequently seen

in Mauritius, less so in Calcutta. It appeared about a week after the œdema and lasted from ten to twelve days. On the skin, vascular nævi often appear and may bleed profusely, while telangiectases are common. De and Chatterjee described the eruptions as "nodular," resembling sarcoids, in some epidemics, while lesions on the mucous membranes have been noted. They do not inconvenience the patient, but may bleed uncontrollably. Ecchymotic patches consist, not of hæmorrhage, but of telangiectases. Three to six weeks after the first symptoms, nodular excrescences are seen; there may be 100 or more

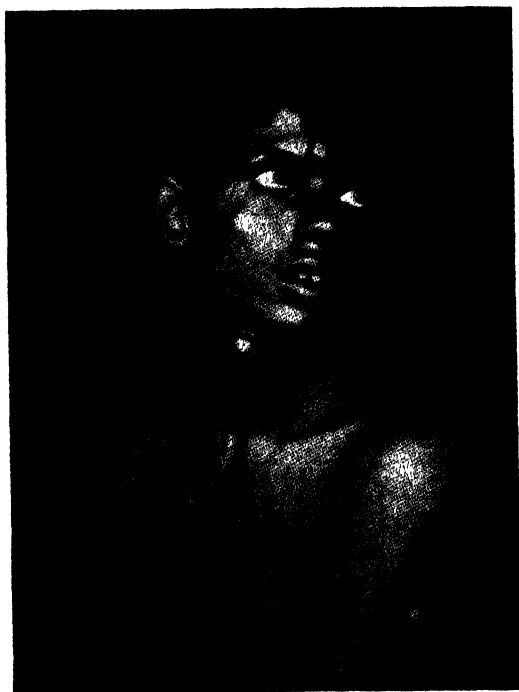


Fig. 231.—Nodular lesions (sarcoids) in epidemic dropsy. (*After De and Chatterjee*)

they may be sessile or pedunculated, varying in size from a pea to a lemon, and they bleed readily (Fig. 231).

Disturbances of the heart and circulation are prominent in nearly all the cases. The pulse is weak, rapid and irregular, the blood-pressure low; cardiac bruits are often noted. Breathlessness on exertion occurred in all cases, severe orthopnœa in many. Signs of pleural and pericardial effusion, of œdema of the lungs, of pneumonia, and of cardiac dilatation are common. Hawes stated that the lung signs are characteristic and resemble a bronchial spasm with defective aëration. Anæmia is usually marked, and so are wasting and prostration. The urine is not albuminous, but of low specific gravity and greatly increased in amount. Concurrent primary glaucoma is not uncommon (Kirwan).

Diagnosis.—It may be necessary to differentiate epidemic dropsy from the war œdema as observed in Central Europe and Egypt during the 1914–1918 and

1939-1945 wars. The latter occurred in a population undergoing dietetic restrictions, and was characterized by great emaciation and a high degree of anaemia. Experiments with rats fed on diets deficient in proteins and salts produce a condition not unlike nutritional oedema. From oedematous beriberi the disease is differentiated by pyrexia, the peculiar erythematous rash, and persistence of the deep reflexes. A history of family outbreaks following the use of mustard oil suggests epidemic dropsy. Not all batches of oil are contaminated with argemone oil.

Treatment is based upon the facts: (1) the adulterant argemone oil is the primary cause; (2) that it is a cumulative poison; (3) that it causes capillary dilatation and permeability; (4) the serum albumin and calcium are reduced, whilst serum globulin is increased; (5) carbohydrate metabolism is checked at the pyruvic acid stage; (6) myocardial damage is set up. Antihistaminic drugs, such as phenegan, benefit, though no rise in blood histamine has been demonstrated. Restoration of damaged capillaries by vitamins C, E and P, protection of the liver by a diet rich in protein and fat with glucose and insulin (10 units twice daily) is indicated. The calcium deficiency is restored by 10 per cent. calcium sandoz intravenously.

VENO-OCCLUSIVE DISEASE OF THE WEST INDIES

A new entity has been described by Stuart and Bras (1955) in the liver of adult Jamaicans.

Hepatomegaly and ascites are brought about by occlusion of the hepatic venous radicles. Improvement takes place on a high protein diet and salt restriction. A similar disease has been found in Barbados and in fact it is found to be widespread in animals. It has been known since 1920 that *senecio* (ragwort) produces fibrosis and cirrhosis of the liver in cattle and horses, while similar conditions are the "walking disease" of both these animals in N. W. Nebraska, the "walk-about disease" in N. W. Australia, the "Winton disease" in New Zealand and "dunsiekte," or enzootic liver disease of equines in S. Africa.

Bras, Bery and György (1957) brought forward evidence that herbal infusions made with *Crotalaria fulva* (rattlebox), a plant commonly used as an ingredient of bush teas, is the probable cause. The toxic origin of this disease was originally suspected by McFarlane and Branday in 1945. The disease has been produced in calves and the liver lesions differ in several respects from the mild hepatic injury seen in kwashiorkor.

Hill, Stephenson and Filshie (1958) have collected much evidence that the disease is initially caused by the pyrrolizidine group of alkaloids in *senecio*, *crotalia* and *heliotropum* and it has now been reproduced in rats injected with monocrotaline (91.7 mgm. per kgm.). Monocrotaline ($C_8H_{23}O_6N$) is one of the pyrrolizidine group of alkaloids isolated from several species of *Crotalaria*.

Within ten days hepatic reno-occlusive disease developed with internal thickening of the centrilobular veins causing partial or complete occlusion and lagoons of blood within the sinusoids.

CHAPTER XLIX

ANIMAL POISONS

POISONOUS SNAKES

SNAKES form a sub-order of the reptiles and have definite characters. The quadrate bone is articulated to the skull, but there is no tympanic cavity. The brain-capsule is osseous, and the mandibles are united mesially by a highly elastic ligament. The limb girdles are absent or reduced to mere vestiges. A peculiar feature is that there are no movable eyelids, but the eyes are covered with a transparent disc, which is shed with the rest of the epidermis. The tongue is deeply bifid and is retractile

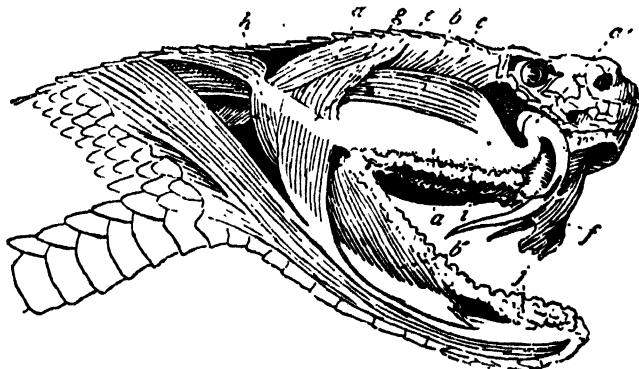


Fig. 232.—Poison apparatus, venom gland, and muscles of rattlesnake (lateral view).
(After Duvernoy, in Boulenger's "Snakes of Europe.")

a, Venom-gland; a', venom-duct; b, anterior temporal muscle; b', mandibular portion of same; c, posterior temporal muscle; d, digastric muscle; e, posterior ligament of gland; f, sheath of fang; g, middle temporal muscle; h, external pterygoid muscle; i, maxillary salivary gland; j, mandibular salivary gland.

into a basal sheath; but is protrusible when the mouth is closed through a notch in the rostral shield (Fig. 232). As in the lizards, the anal cleft is transverse.

Characters used for identification and classification.—Osteological and dental characters are employed to determine families and genera, and it is therefore necessary to understand the various types of ophidian skulls and the different arrangement of fangs and solid teeth. For generic and specific distinctions the form and number of the epidermal shields and scales are of great importance.

The arrangement of the scales on the head is shown in Fig. 233, and that of the prefrontal and preocular scales varies in different species and genera. In the crotalinæ, or pit vipers, there is a sensory uveal pit situated between the eye and the nostril. Viperine snakes can generally be distinguished from the colubrinæ by their smaller size, the angular shape of the head, and the sharp stumpy tail. The maxillæ are vertically erectile, with enormously enlarged tubular fangs situated anteriorly (Fig. 234).

The more important poisonous snakes.—The poisonous snakes are distributed among the following families and subfamilies:—

- (a) *Viperidae*, or true vipers, found only in the old World.
- (b) *Crotalidae*, or pit vipers, found in the New World and in Asia.
- (c) *Elapinae*, represented by coral snakes and cobras, found in all continents, except Europe.

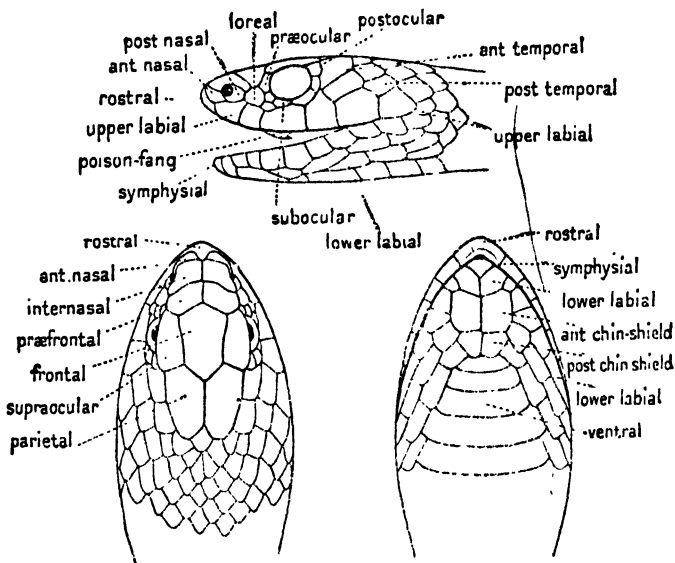


Fig. 233.—Head-shields of *Causus rhombeatus*.
(After Boulenger, "Proc. Zool. Soc." 1915.)

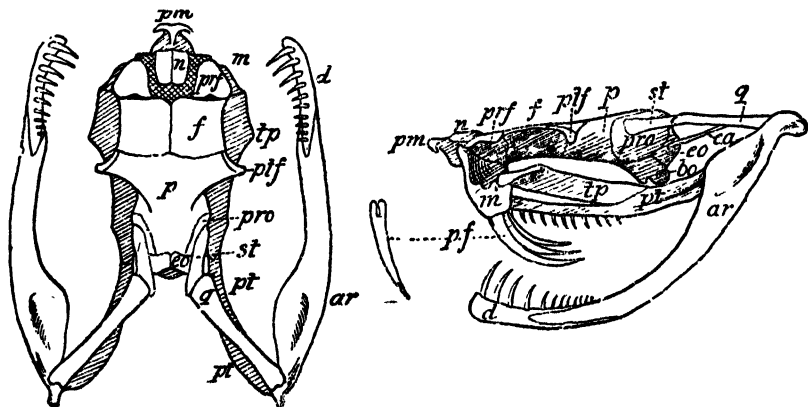


Fig. 234.—Skull of *Trimeresurus gramineus*, upper view and side view. (After Boulenger, "Vertebrate Fauna of the Malay Peninsula; Reptilia and Batrachia.")

ar, Articular; ho, basioccipital; ca, columella auris; d, dentary; eo, exoccipital; f, frontal; m, maxillary; n, nasal; p, parietal; pf, poison-fang; pm, premaxillary; prf, præfrontal; pro, prootic; pt, pterygoid; ptf, postfrontal; g, quadrate; st, supratemporal; tp, transpalatine.

(d) *Colubridæ*, to which nearly two-thirds of the known species of snakes belong, but in which the only poisonous varieties are some of the rear-fanged reptiles seldom found outside Africa.

(e) *Hydrophinae*, or sea snakes, which are so unobtrusive in their habits that they rarely conflict with man.

Africa.—The annual snakebite death rate is about 0.4 per 100,000 population. The following are the most frequent causes of death: *Viperidæ*: *Bitis* (*arietans*, *gabonica*, *nasicornis*), *Echis carinatus*, *Causus rhombeatus*.

Elapidæ: *Naja* (*nigricollis*, *melanoleuca*, *haje*): *Dendraspis* (*augusticeps*, *jamesoni*, *viridis*).

The Americas.—Two families, the *Crotalidæ* and the *Elapidæ*, are present in U.S.A. The pit vipers (*Crotalidæ*) are abundant and the presence of 85 species and sub-species has been established, including the true rattlesnakes, the pigmy rattlers and the "massasauga" of the genus *Sistrurus*, the "copperhead" (*Ancistrodon mokeson*) and the "water moccasin" (*A. piscivorus*). The family *Elapidæ* is represented by coral snakes. Poisonous snakes are more abundant in South and Central America than in Northern America. In the two former, the majority of fatalities are caused by members of the *Crotalidæ*, especially the tropical rattlesnake (*Crotalus durissus terrificus*) and the members of the genus *Bothrops* (*B. atrox*) or "fer-de-lance," *B. jararaca*, *B. schlegeli*, and the bushmaster (*Lachesis muta*).

In Brazil the number of annual snakebite deaths is about 2,000 (a death-rate of 4 per 100,000).

The large majority of deaths occur from the bite of *C. terrificus*, *Bothrops jararaca*, *B. jarara-cassu* and *B. alternata*.

In Trinidad, Tobago and West Indies, the most poisonous species is *B. atrox* (*fer-de-lance*). The coral snake (*Micrurus corallinus*) is also found.

Asia.—All families containing venomous snakes are represented from West Pakistan to Malaya. The region includes countries with the highest snakebite death rates in the world.

The vast majority of deaths are caused by *Viperidæ* (true vipers) and the *Elapidæ* (cobras and kraits).

In Burma an average of 2,000 deaths from snakebite are registered every year. The mortality is highest there, where the annual snakebite death rate is about 15.4 per 100,000 population.

The majority of deaths are caused by Russell's viper, or "daboia" (*Vipera russelli*).

Cobras and kraits (*Bungarus*) account for the large proportion of the snakebite mortality. In Ceylon the death rate is 4.2 per 100,000. Russell's viper (*Vipera russelli*), the cobra (*Naja naja*) and the Indian krait (*Bungarus candidus*) are the most dangerous.

India and Pakistan.—In India, before partition, the recorded snakebite deaths were from 10,000 to 15,000 a year. Now the annual death-rate from snakebite is 5.4 per 100,000 population. The largest number of deaths are reported from Bengal, Uttar Pradesh, Madras, Bombay and

Bihar. The area of highest snakebite mortality is in W. Bengal in the Delta of the Ganges, in certain districts, Dinajpur, Nadia, Murshidabad and Midnapore.

Cobra (*Naja naja*, *N. hannah*, or "hamadryad"), "Krait" (*Bungarus candidus*), *B. fasciatus*, Russell's viper or "daboia," and *Echis carinatus* are the commonest terrestrial poisonous snakes in India and Pakistan. There are a few other species of poisonous snakes, such as the green pit viper (*Trimeresurus gramineus*), the coral snake (*Calliophis*) and the Himalayan pit viper, *Ancistrodon*, which seldom inflict fatal bites.

In Thailand (Siam) deaths from snakebite total 1.3 per 100,000.

The large majority occur from the bites of the cobras (*Naja naja* and *N. hannah*), kraits (*Bungarus candidus*, *B. fasciatus*), coral snakes, *Calliophis*, *Doliophis* and Russell's viper.

Oceania and the Pacific.—Poisonous snakes are found in Australia, New Guinea, in the Solomon Islands and in relatively fewer numbers in the Philippines and in Japan.

Australia.—There are over 70 poisonous snakes. The most aggressive is the tiger snake (*Notechis scutatus*), which is responsible for a high percentage of the deaths. The "taipan" (*Oxyuranus scutellaris*), and the "death adder" (*Acanthophis antarcticus*) are specially active and dangerous in the sandy areas. The brown snake (*Demansia textilis*) and the Australian black snake (*Pseudechis porphyriacus*) are widely distributed.

In Papua and New Guinea the most dangerous are the "death adder" (*Acanthophis antarcticus*), the brown snake (*Demansia textilis*) and the black snake (*Pseudechis porphyriacus*).

In Japan the "mamushi" (*Ancistrodon blomhoffi*) is the most common poisonous snake.

Africa.—It is estimated that the annual snakebite deaths average 800 which gives the death rate of 0.4 per 100,000. There are no poisonous snakes in Mauritius, Seychelles, Madagascar and Comoro Islands.

The following are the most dangerous:

Viperidæ: *Bitis* (*arietans*, *gabonica*, *nasicornis*), *Echis carinatus*, *Causus rhombeatus* or "Night adder." *Elapidæ*: *Naja* (*nigricollis*, *melanoleuca*, *haje*), *Dendraspis* or "Black Mamba" (*augusticeps*, *jamesoni*, *viridis*), (*Dispholidus typus*) or "Boomslang"), the ringhals or spitting cobra (*Sepedon hemachales*).

Europe.—The only poisonous snakes found in Europe and in N. Asia belong to the family Viperidæ. Of this family the common viper or adder (*Vipera berus*) is most extensively distributed, and is the only poisonous species in the British Isles. The asp (*V. aspis*) is found in S. France, S. Italy, Yugoslavia, the Apennines and Pyrenees.

The long-nosed viper (*V. ammodytes*) occurs in Austria, Bosnia and other Balkan countries. *V. renardi* is found in the Crimea and parts of E. Russia extending into Central Asia.

It is estimated that 50 deaths occur annually due to bites of vipers in Europe.

The poison apparatus consists of a pair of venom-secreting glands connected by ducts to the poison-fangs in the maxillæ; they are analogous

to the parotid glands in mammals. These glands, situated in the temporal regions, are operated during the act of biting, when they are squeezed by the contraction of the temporal muscle, the venom being expelled by means of the grooved or tubular fangs. (Fig. 232.) In the African "spitting cobras" the venom, which contains an active hæmolytic and anticoagulant factor, is ejected with great force into the face of the enemy.

In striking, the snake throws itself forward with great violence. On the whole vipers strike with greater velocity than colubrids. Most strike with the jaws closed, but as the head approaches the victim, the mandibles are depressed by rapid contraction of the digastric and other muscles and simultaneously the fangs are elevated and rotated forward. The fangs of colubrids are grooved and shorter than those of vipers. Closure of the jaw is brought about by the simultaneous contraction of the temporal muscles which strongly elevate the mandible (Fig. 235). In

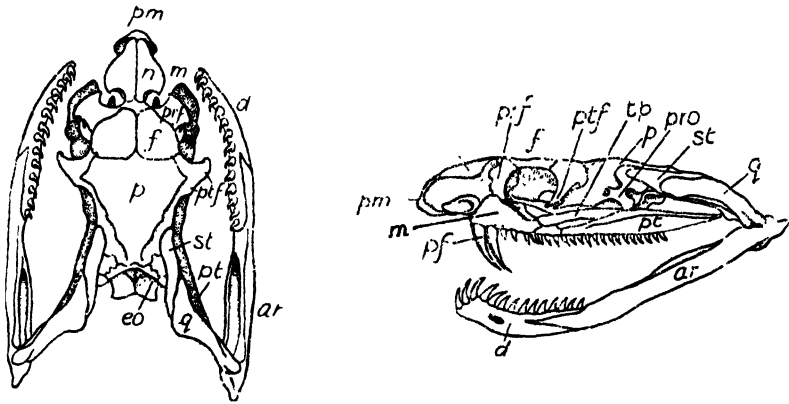


Fig. 235.—Skull of *Naja naja*, upper view and side view.
(After Boulenger, "Catalogue of Snakes," vol. iii.)

ar, Articular; d, dentary; eo, exoccipital; f, frontal; m, maxillary; n, nasal; p, parietal; pf, postfrontal; p, parietal; pro, prootic; pt, pterygoid; pf, postfrontal; q, quadrate; st, supratemporal; tp, transpalatine.

vipers, expulsion of the venom is instantaneous, and independent of fixation of the lower jaw. Immediately after the insertion of the fangs and accompanying discharge of venom, contraction of the retractor muscles drags the elevated fangs downwards and backwards through the tissues. Impression of the fangs and the pterygo-palatine indentations may be made in Kerr's impression compound of dental wax, and by this method it has been found that the distance between the fang punctures affords a fair index to the venom-yield. Death may follow inoculation from a single fang (Fairley).

The lethal dose of venom varies within wide limits when tested on different species of animals. The killing capacity of different venoms for sheep, estimated in terms of average venom-yield, was found by Fairley to be: 118 for the Australian tiger snake (*Notechis scutatus*), 31.7 for the cobra, 2.2 for Russell's viper, 84.7 for the Australian death-adder (*Acan-*

thopis antarcticus), 8·9 for the copperhead (*Denisonia superba*), and 1·5 for the black snake (*Pseudechis porphyriacus*).

The *venom*, a clear, amber-coloured fluid, is composed of modified proteins. It is of two kinds; that of the *Viperidæ* (vipers) acts principally upon the vascular system, but that of the *Colubrinæ*, *Elapinæ* and *Hydrophinae*, i.e. cobras and sea-snakes, acts upon the nervous system and brings about respiratory paralysis. The complexity of venoms is determined by physical methods, such as electrophoresis, cross-neutralization tests with different venoms and anti-sera. Those of one venom can neutralize those of other snakes belonging to the same family. There is more than one proteolytic enzyme in cobra venom and also ferments, a proteolytic, hæmolytic and a phospholipase. A venom, in general, consists of a mixture of several individual proteins which constitute 90–92 per cent. of its dry weight. Elapine venom contains a highly potent neurotoxin: cobra venom a hæmolysin. A cardiotoxin has also recently been isolated by Sarkar (1956). Death from cobra bite is caused primarily by the failure of respiration due to paralysis of the respiratory centres. The presence of an acetylcholine as a hydrolyzing enzyme has been proved by Iyengar.

Hyaluronidase, as a spreading factor, is present in most venoms and is surprisingly high in that of the common krait (*Bungarus cæruleus*).

Snake venoms have a profound effect on blood coagulation and usually hasten the clotting process. Russell's viper venom has a prothrombin-like property and it has been shown that calcium plays an important part in the clotting of fibrinogen when snake venom is used as a clotting agent.

The toxin of the venom of the tropical rattle-snake (*Crotalus t. terrificus*) contains *crotamine* which produces paralysis in experimental animals. It is composed of a proteolytic enzyme which clots fibrinogen and a neurotoxin which corresponds to *crototoxin*.

Naja nigricollis in S. Rhodesia and S. Africa is one of the spitting cobras and can eject venom as far as six feet and can aim at the eye of its victims. It causes extremely painful conjunctivitis which subsides only after several days. The eye should be washed out with milk alone or in a solution of potassium permanganate and a few drops of antivenene instilled into it.

Symptoms of snake-bite in man.—The physiological action and symptoms produced by snake venoms can be classified into two groups, colubrine and viperine.

1. *Colubrine*.—In cobra-bite (Fig. 236) (*Naja naja*) there is severe pain and the part becomes inflamed and œdematous. After an hour the patient becomes dull, apathetic, and unable to stand. Nausea and vomiting, with profuse salivation and paralysis of the tongue or larynx, supervene. Soon, the respiratory centre becomes involved, and respiration ceases entirely. Should the patient survive the paralysis, recovery is rapid. The pupil is contracted throughout. The king cobra, or hamadryad (*Naja bungarus*), is the most formidable and aggressive of all the cobras.

The bite of the krait (*Bungarus fasciatus*, Fig. 237) is extremely dangerous, especially in Northern India; the symptoms are similar to those produced

by the cobra. *Dendraspis viridis*, a very agile and aggressive species, is regarded as the most dangerous of African snakes.

The symptoms caused by the bite of the Australian colubines may not be very severe, but constitutional effects appear with great rapidity—sometimes in as short a period as fifteen minutes. A feeling of faintness and irresistible desire to sleep are soon followed by paresis of both legs, vomiting and cardiac paralysis. The pupil is widely dilated and insensitive to light. Should the patient survive the coma, recovery is complete and no sequelæ occur.

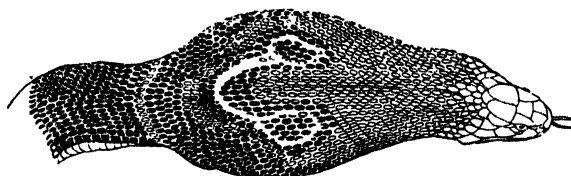


Fig. 236.—The cobra (*Naja naja*).

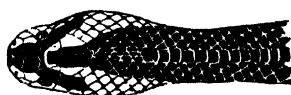


Fig. 237.—The krait (*Bungarus fasciatus*).

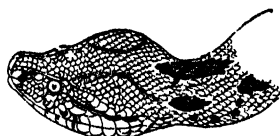


Fig. 238.—The daboia (*Vipera russellii*).

2. *Viperine*.—For the type of lesion produced by the viperines, that of Russell's viper, the daboia (*Vipera russellii*, Fig. 238) may be taken as an example. This species is extremely deadly; the bite causes severe pain with rapid and extensive cedema, together with blood-stained discharge, and ecchymoses around the site of the punctures. Collapse, small thready pulse, nausea and vomiting, and dilated, insensitive pupils, soon supervene, together with a loss of consciousness, more or less complete, from which temporary recovery sometimes occurs. Should the effects of the now diffused toxin wear off, the local condition of the wound becomes aggravated; extensive suppuration and sloughing, malignant cedema, or even tetanus and hæmorrhages from the mucous surfaces—hæmaturia or melæna—may supervene. There is no paralysis of the muscles, but Rogers showed that viperine toxin produces vasomotor paralysis. It is more easily destroyed by caustic agents than colubrine venom.

The bite of *Echis carinatus* (Fig. 239) is less dangerous than that of the daboia, but is in many ways similar in its effects.

The bites of the rattlesnakes—*Trimeresurus* and *Crotalus* (Figs. 240, 241)—are remarkable for the local disturbance they produce. Constitutional paralytic symptoms come on quickly, usually in less than fifteen minutes. Should the patient recover, swelling and discoloration extend up the limb and trunk, and general symptoms of blood-poisoning with pyrexia, restlessness and delirium set in. The wound suppurates freely and may become hæmorrhagic, or even gangrenous.

The symptoms produced by the bite of the European vipers resemble those of *Crotalus*, but are very much milder.

The mortality from snake-bite, even of the most venomous varieties, is not so great as is popularly supposed, and is estimated at about 30 per cent. That it is not more is probably due to the fact that the reptile is seldom able to inject a full dose of venom. If given a fair chance, the cobra is able to inject the equivalent of twenty lethal doses at a time.

Sea Snakes

Sea snakes inhabit the shores of the Indian and Pacific oceans, ranging from the Persian Gulf to S. Japan, the coast of tropical Australia and the S. Pacific Isles.

These snakes can be identified by their flat, rudder-like tails. Water snakes, which are also common along these shores, are harmless and have round tapering tails.

The commonest sea snake is *Enhydrina schistosa* which is 3-4 ft. (0.9-1.2 m.) and about 1-2 in. (2.5-5 cm.) thick and recognizable by a deep



Fig. 239.—The phoosa (*Echis carinatus*).



Fig. 240.—Rattlesnake (*Trimeresurus lanceolatus*).



Fig. 241.—Rattlesnake (*Crotalus terrificus*).

Above, tail with "rattle."

cleft in its chin. Some species of *Hydrophis* grow to the length of 9 ft. (2-7 m.), but are relatively slender, with small heads.

Members of the genus *Astiotia* are mostly massive, being up to 4 in. (10 cm.) thick.

Pelamis platurus has the widest distribution and is recorded off the West coast of tropical America and the shores of S.E. Africa. The genus *Laticauda* is amphibious.

The venom of these sea snakes has been proved twice as toxic as that of the cobra, and it is purely neurotoxic; but cobra antivenene is quite ineffective.

Victims are usually fishermen. Bathers and paddlers in shallow water do not usually see the offending snake.

The symptoms are due to bulbar and motor paresis which is usually flaccid, but may be spastic. Jaw trismus is an outstanding feature. Dysarthria and dysphagia are common. Albuminuria is usual. Failing vision is regarded by Malayan fishermen as a fatal sign. In less severe cases trismus, ptosis and peripheral paralysis appear. Diagnosis is

facilitated by fang marks usually around the ankles, but bites are often inconspicuous. There is complete absence of pain.

Although specific antivenene is not yet available, a polyvalent serum with a *krait* fraction should be used. 20 ml. is slowly injected intravenously, preceded by cortisone to prevent serum reactions. (Reid, 1956.)

Diagnosis.—The difficulties of diagnosis are many, especially in primitive peoples, where it is difficult to obtain a description of the species of snake involved. In India it is generally fairly easy to diagnose that snake bite has occurred, though it may be difficult to distinguish between krait and cobra bites. When a definite description is given of a bite by a hooded snake poisoning can be attributed to cobra venom. There is, it must be admitted, no single symptom, or sign pathognomonic of one or the other for they do not necessarily appear in any definite pattern. Considerable variation is met with, depending on the amount of venom injected, the size of the snake, and the age and physical resistance of the victim.

Perhaps the most useful sign of viperine poisoning is the lessened coagulability of the blood, so much so that if the patient is seen more than half an hour after being bitten, viper bite can most certainly be ruled out, if the blood coagulates in less than 10 minutes. The routine practice should be to carry out a blood coagulation test in all cases of snakebite and, as the result, many patients can be discharged without serum treatment.

Some cases are undiagnosable on symptoms, but where delayed coagulation occurs, the timely administration of serum is a life-saving measure. The return of coagulation time to near normal is associated with an improved prognosis.

Examination of the urine for presence of red blood cells may provide the clue to the true nature of the biting snake.

In the absence of any clear-cut symptoms this is often the first clinical sign of a viper bite.

Treatment.—To be effective, all treatment should be vigorous and prompt. It should be directed, first, to prevent absorption of the poison; secondly, to neutralize, as far as possible, its toxic effects. A ligature should be tied around the limb, immediately above the bite; for this purpose, if it is at hand, a stout india-rubber band, firmly applied, is the best ligature, or strips of clothing may be loosely knotted round the limb and subsequently tightened by twisting with a stick. It has been shown that by *local venesection* one-half to one-third of the injected venom can be removed. It is generally held that bites on the fingers and toes are more dangerous than those inflicted on broad, flat surfaces, as the calf or thigh. This is to be attributed to the supposed difficulty experienced by the snake in closing the lower jaws on such surfaces, hence in such a situation the reptile is believed to inject the full dose of venom. Snakes, especially the poisonous varieties, are nocturnal or semi-nocturnal and it is generally believed that snake bites are more common in the night than in the daytime. However, it has been shown that the cobra bites just as frequently during the day as during the night.

These measures, if applied within a few minutes, are generally approved.

Incisions and the application of *potassium permanganate* crystals, which constitute such a general and popular method, should be abandoned.

It is doubtful whether any form of treatment is of benefit, unless applied immediately. Thus amputation of the part above the bite has proved effective, if performed *immediately*. Alcohol and strychnine, formerly regarded as antidotes, are now known to be inefficacious. Carbolic or Lifebuoy soap (or indeed any soap) is a practical method of first-aid treatment. It is given in 5 per cent. solution, by infiltration, into the site, to a depth of not more than $\frac{1}{2}$ in., *in the vicinity* of the fang marks, in quantities not exceeding 2 ml. For a bite on a digit a few drops and for those on the leg up to 2 ml. suffice. This treatment may result in an ulcer. Carbolic soap solution appears to detoxify only cobra and krait venoms, but has no action on Russell's viper venom, and it must be supplemented, as early as possible, by serum treatment. Recent work in the S. African Institute of Medical Research has confirmed the value of the soap method in the case of the S. African cobra (*Naja flava*) and ringhals or "spitting cobra" (*Sepeodon haemachates*) venoms.

Heparin.—What is needed is anticoagulant therapy. For a short time after injection of Russell's viper, or Echis venom, the clotting time is decreased. At this time fibrin is deposited in the capillaries. Later the clotting time becomes more and more prolonged and finally the blood becomes incoagulable and hæmolysis results. It has been shown that laboratory animals may be saved by heparin. It is therefore indicated, but it cannot take the place of specific serum.

Stahnke, Allen (1957) and others advocate immediate ligature followed by *cryotherapy*—that is the immersion of the affected limb in a 5 gallon can filled with water. The steps are as follows:

(1) Place a ligature between the bite and the body. Cover the bitten area with ice. (2) Immerse the limb above the bite in iced water and after not less than 5 minutes remove the ligature, keeping the limb in water for 2 hours. (3) Pack the limb in finely crushed ice for 24 hours which prevents the absorption of the neurotoxic factor and also stops the pain.

In S. and C. Africa the night adder (*Causus rhombeatus*) usually bites on the foot. The foot should be soaked every 4 hours in a hot solution of potassium permanganate and glycerine and ichthyol dressings applied. 10 ml. of a 10 per cent. calcium gluconate should be given intravenously and repeated at intervals of 8 hours to relieve the pain.

The greatest care should be taken with tourniquets. To be effective it should occlude the arterial circulation and must therefore be released for 1-2 minutes every 20 and should be removed altogether $1\frac{1}{2}$ hours after the serum has been given. The psychological element induced by natural fear of snakes usually requires urgent action and the administration of potassium bromide or phenobarbitone.

Cauterization of the wound should never be performed.

Serum therapy.—The absorption time of lethal doses of snake venom has been determined by experiment. Acton and Knowles injected 100 mgm. of cobra venom into the tips of the tails of four dogs and am-

puted them 7.6 cm. above the site of inoculation at one-minute intervals. All the animals died within a period of 45-85 minutes.

It has long been known that immunity could be produced in animals by repeated and progressive inoculation of venom; and a similar result is produced in those who have been repeatedly bitten by snakes. This immunity, however, is specific only for the venom of that particular species. Calmette attempted to produce, in *antivenene*, a serum active against all snake venoms, but his claim has not been substantiated.

The serum prepared against cobra venom is found to be anti-toxic to the homologous venom, and to a certain extent to that of *Bungarus fasciatus*, but is without action on the viperine venoms of daboia, *Echis*, *Trimeresurus*, and *Crotalus*. The serum produced against daboia venom has no action whatever upon the venoms of *Naja*, *Bungarus*, etc. On the other hand, it has been shown that the hæmolytic properties of Indian and African cobra venoms are practically identical, and the antivenene prepared in India against *Naja naja* is equally serviceable against *N. flava*, and that prepared in South Africa against *N. flava* acts similarly against the former.

In practice the very important drawback to use of antiserum is that, though specific towards some other species of snakes, it may be impotent for the particular species concerned. The practical method of meeting this unfortunate circumstance is to issue an antiserum effective against the most common and the most dangerous snakes in any given district.

All antivenenes are relatively weak in their action as compared to antidiphtheritic and antitetanic sera. The antivenene should be injected intravenously in large amounts as soon after the bite as possible. Acton and Knowles demonstrated that such a serum must be given before the minimum lethal dose of venom has been absorbed, and that it requires some ten minutes to find its way into the circulation. The injection should be made *intravenously*, and at least 20-30 ml. should be given. In India serum treatment, if available, should be employed in every case, on the chance that the snake concerned was either cobra or daboia. The longer antivenene is withheld, the greater is the dose required to save life. In cobra poisoning the administration of antivenene, even in far-advanced cases, can neutralize the venom without any residual paralysis. After complete investigations of indigenous and other remedies the conclusion has been reached that there is no antidote which can so effectively neutralize venoms of poisonous snakes as can antivenom.

There is still much work to be done before an efficient polyvalent serum can be produced. One of the difficulties is that every injection of venom into the horse for the production of immunity gives rise to abscess-formation, and that the whole process lasts from a year to a year and a half. It is estimated that in Brazil the death rate from snake-bite has, by prompt antivenene treatment, been reduced from 25 to 2.5 per cent.

In the Central Research Institute at Kasauli the preparation of antivenene is a concentrated and purified globulin solution specific for the venoms of the Indian cobra (*Naja naja*) and the daboia (*Vipera russelli*). The therapeutic efficiency is strikingly shown, when deaths among 131 cases of cobra bite (8.4 per cent.) and those among 62 cases of Russell's

viper bite (11·8 per cent.) are compared with the mortality among 85 cases of krait bite (77·1 per cent.) and 158 cases of *Echis* bite.

Differences exist in the quantity of venoms from different snakes of the same species or even from the same snake at different times of the year. The greatest increase in the incidence of bites is during the hottest months of the year: the peak being reached in July and August.

Other measures.—Cortigen, suprarenal cortex hormone extract, is used with some success in the treatment of bites of the Malayan pit viper (*Ancistrodon rhodostoma*). Cortigen is given orally in 25 mgm. tablets. During the first 24 hours it is given four-hourly and during the next equal period, six hourly. In cases of shock Reid advocates generous blood transfusions.

VENOMOUS LIZARDS

All lizards are absolutely non-poisonous, with the exception of a single genus, easily recognized, inhabiting Mexico and Arizona. *Heloderma* consists of two species, *suspectum* and *horridum*, both heavy, stout lizards, yellow or shrimp-pink in colour, with black bead-like scales. They are desert-dwellers, and store

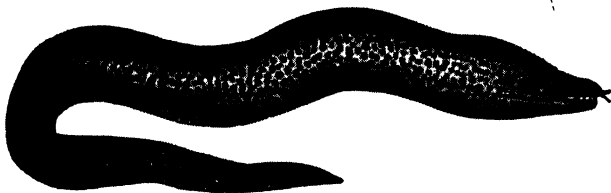


Fig. 242.—*Muræna moronga*. (After Calmette.)

fat in their swollen tails to tide them over periods of famine. Popularly known as the "Gila¹ monsters," they were first discovered near the village of Gila.

The poison apparatus is in the lower jaw, where venom-secreting submaxillary glands are connected by ducts with grooved teeth. Symptoms of poisoning start with paralysis. A large dose produces dyspnoea and convulsions. Post-mortem examinations on experimental animals show a greatly dilated heart and venous congestion of the internal organs. Changes in the spinal-cord ganglion cells have also been observed.

Tyler (1956) has shown that an auto-antigenin occurs in the blood serum and liver and resides in the globulin fraction.

POISONOUS FISHES

Poisonous fishes exist in most tropical waters, especially among the coral reefs of the Pacific and Indian Oceans. Their venom may be conveyed to man either through the bite or by stings. In one case the poison is secreted by certain epithelial glands within the mouth; in the other, by poison-glands connected with barbs in the dorsal fin. The former comprise more than one hundred species of the genus *Muræna*, all of which possess powerful teeth capable of inflicting bites (Fig. 242). The poison secreted by the glands courses down the hollow teeth. The effect of the venom on man is neuro-cardiac. The latter contains a great number of widely separated genera. In some, the poison finds its way to the exterior only when the barbs are broken, and produces severe inflammation

¹ Pronounced "heela."

in the wound and, it may be, tetanic symptoms. *Synanceia*, a spinous genus is widely distributed throughout the Indian and Pacific Oceans, and is one of the Scorpænidæ (scorpion fish); *S. verrucosa* is the most toxic. The poison apparatus is connected with the dorsal fin. *Plotosus anguillaris*, known as "machoir" in Mauritius, has a similarly wide distribution; while *Saccobranchus fossilis*, in the waters of India and Ceylon, produces much the same symptoms.

Stingrays are common. The tropical species is *Aetobatis narinari*. The venom is secreted by the glandular epithelium sheath of caudal sting. Death may ensue. Treatment is effected by washing out the wound with 5 per cent. potassium permanganate solution.

Over forty species of *Scorpena* are found in tropical waters. Their integument is provided with numerous rays, the stings of which may excite convulsions and even cause death. The symptoms usually evoked are pain extending up the limbs, profuse sweating, pallor, dyspnoea and tachycardia. There is often also a morbilliform or scarlatiniform rash. Symptoms are controlled by local injection of 5 per cent. potassium permanganate and pain can be mitigated by infiltration of 2 per cent. procaine and 1 in 1000 solution of adrenalin.

In South American waters, several species of *Thalassophryne* have dorsal spines containing a central poison-duct connecting with glands. Species of *Trachinus* (Weeverfish), in northern waters as well as in the Mediterranean, have two sets of poison barbs situated on the operculum as well as on the dorsal fin. The venom has a general action on the heart, besides causing severe pain and mydriasis.

Toadfish stings are caused by *Batrachus grunniens* in W. Indies tropical waters and by *Thalassophryne dowi* on the Pacific Coast of Panama.

POISONING FROM INGESTION OF POISONOUS FISHES

Cases of fish-poisoning arising from eating the flesh of fishes containing some intrinsic toxin occur more commonly in the tropics than in more temperate countries. In many instances these fish may be eaten with safety, except at certain seasons of the year; in others the poisonous qualities are acquired only after feeding or living in certain localities.

The barracouta (*Sphyræna barracuda*), a pike-like fish, is eaten widely throughout the South Atlantic; it is the large examples, especially those that are spawning, which are apt to be poisonous, and the symptoms are mainly gastrointestinal, with paræsthesia. Natives regard as poisonous fishes which show a whitish, watery fluid when cut up, or a black, purplish discoloration at the base of the teeth.

In these waters Ciguatera poisoning results from eating *Sphyræna picuda*; within a few hours of ingestion, abdominal pain, diarrhoea and vomiting ensue.

There are various sprats (*Clupidæ*) in tropical waters which acquire poisonous properties; among them is *C. longiceps*, a sardine found in Ceylon waters, which occasionally may produce collapse and even death.

Many species of the widespread genus *Tetodon* are poisonous, such as the "death-fish" of Hawaii—*T. hispidus*—while other species occur in Japanese and Korean waters. The poison is contained in ovaries and eggs, and causes gastrointestinal and nervous symptoms, sometimes culminating in syncope or coma. The toxic principles are *tetodotoxin* and *spheroidene*.

The flesh of certain large fishes normally constituting excellent food, such as the king-fish (*Scomberomorus cavalla*), may occasionally exhibit toxic properties.

In all forms of fish-poisoning the most effective treatment is to evacuate the poison by washing out the stomach and administering purgatives. Other symptoms must be treated on general lines with stimulants, hot-water bottles, and injections of morphia, if necessary, to alleviate pain.

POISONOUS SHELLFISH

In the South Pacific Islands fatal cases of poisoning may be due to bites of certain shellfish of the genus *Conus*, all of which are adorned with brightly-coloured shells. Six at least are known: *Conus tulipa*, *C. marmoreus*, *C. striatus*, *C. geographus*, *C. textilis*, and *C. aulicus*. They are provided with a long tubular proboscis which can be protruded beyond the shell, and opening into it is a sac containing two rows of hollow teeth. According to Clench and Kondo (1943), the poison is not delivered directly from the poison gland, but probably on to the wounded surface. The symptoms are acute pain, swelling, numbness, and spreading paralysis. There may be early drowsiness, dysphagia, deepening into coma and death. When bitten in this manner, the Polynesians make small incisions round the bite to cause blood to flow freely. Fatalities have been reported in North Australia and Polynesia. The first accident producing serious symptoms was reported by Hermitte (1946) from the Seychelles.

Of the Bivalves, Mussels produce paralytic shellfish poisoning—*Mytilus edulis* and congeners. Toxicity is due to dinoflagellates (*Gonyaulax catenella*) in their bodies.

In Japan shellfish poisoning is due to *Venerupis semidecussata*. The toxic principle is venerupin which causes acute yellow and red atrophy of the liver.

MUREX POISONING

Murex brandaris and *M. trunculus* occur mostly on the Syrian coast. The active principle is murexine, a choline derivative allied to adrenalin which produces paralysis of the central nervous system.

ANNELIDA (SEGMENTED WORMS)

The stinging sea-mouse (*Chloaia flava*) is a polychæte which causes lesions in sea-bathers due to its poisonous calcareous spicules (Tweedie, 1953), and is known as the bristleworm. Other species are *C. viridis* in West Indies, *Eurythoe complanta* in Australia and *Hermodice carunculata* in tropical E. America and Gulf of Mexico.

POISONOUS CORALS (ANTHOZOA) AND SEA-ANEMONES

Coral dermatitis results from cuts in the skin which cause indolent lesions from contact with the anthozoa. The surrounding skin becomes red, œdematous and itchy.

Sea-anemones of the genus *Hellenopolypus* and *Aktinion* give rise by contact to sponge-fishers' or "Skevos-Zervos" disease, itching and vesication, pustulation, nausea and vomiting being produced. The toxin acts like cantharides, and the lesions are due to urticating cells in the tentacles. Washing with vinegar and the application of olive oil is the best treatment.

POISONOUS ECHINOIDEA, SEA-URCHINS

In the West Indies, especially Barbados, spiny sea-urchins cause septic lesions on hands and feet from punctures by the spines. The poisonous species are *Tripneustes esculentus* and *Diadema antillarum*, which also have poisonous ovaries and eggs, when symptoms resembling fish allergy are produced. *Diamina setosum* occurs off the African coast to Australia, S. Sea Islands and Japan: *Paracentrotus lividus* in the Azores, Africa and Mediterranean: *Toxopneustes pileolus* in Malaya and Japan: *Sphaerechinus granulosus* in Mediterranean and E.

Atlantic. The venom is injected by globiferous pedicellariæ which have blades with a venom gland attached.

JELLY-FISH POISONING

Medusæ of the genus *Obelia* contain in their ectoderm numerous clear ovoid bodies, the stinging capsules or *nematocysts*, which serve as weapons of offence. The whole apparatus is developed in an interstitial cell (cnidoblast) which, as it approaches maturity, migrates towards the surface and at one point is elongated by a delicate process—the cnidocil or trigger hair. When this is touched the cnidoblast undergoes a sudden contraction and causes an eversion of the thread, at the base of which are minute barbs, which are poisonous and produce a numbing effect. The stings produce a painful local swelling and a disagreeable urticaria, and, in susceptible individuals, shock and collapse.

The Portuguese man-of-war (*Physalia*) or “*agua viva*” is provided with a characteristic stinging apparatus. From the underside of the float there hang filamentous tentacles (gastrozooids, dactylozooids and branching blastostyles), some of which are long and retractile and contain batteries of stinging capsules which produce severe dermatitis and irritation in the skin of those who come into contact with them. Extract of the tentacles contain 5-hydroxytryptamine, a potent causer of pain and a releaser of histamine. It is a vasodilator, and is found in wasp venom, and in the stinging hairs of nettles. Anti-histamine cream is curative.

Gymnothorax poisoning of which there are several species, in Red Sea, Indian Ocean and Tropical Pacific. *G. javanicus* is found as above; *G. meleagris*, *G. pictus* and *G. petelli* range to Japan Seas.

Twenty minutes after ingestion there is numbness, laryngeal spasm and aphonia. Mortality is about 10 per cent. Paraldehyde is the best drug to control the convulsions.

SCORPIONS AND SPIDERS (ARACHNIDA)

Scorpions are very common in the tropics, and their stings are very painful and cause a considerable amount of inconvenience, though they are not exactly dangerous, except to young children, in whom, in addition to local symptoms, muscular cramps, profuse perspiration, pyrexia, vomiting and convulsions may be produced. Deaths have been reported from North and South Africa, the West Indies, Mexico, Korea and Manchuria. In Trinidad, glycosuria, hyperglycæmia, pancreatitis, and even pancreatic cysts, are described as sequelæ to scorpion stings. In general the symptoms are lacerymation, salivation and sphincter relaxation.

In Southern Europe and North Africa black scorpions, *Euscorpis italicus* and *Buthus maurus*, in Mexico the “durango” (*Centrurus*), in Brazil *Tityus serrulatus* and *T. bahiensis*, in Manchuria *Buthus martensi*, are dreaded (Fig. 243). In South Africa the genera are *Hodogenes*, *Opisthophthalmus* and *Parabuthus*. In Algeria and N. Sahara the most formidable species are *Androctonus australis*, *Buthus occitanus*, *Buthacus arenicola* and *A. amoreuxi*.

Paired poison-glands are situated in the last or postanal segment of the tail which is jointed and very flexible, so that it can be curved forwards over the

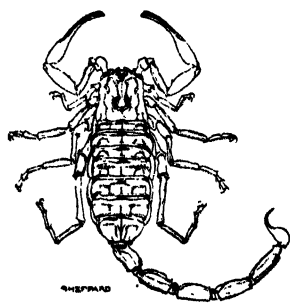


Fig. 243.—Scorpion (*Buthus* sp.). Half nat. size.

body when the scorpion is striking. The venom which it ejects is in many respects like that of the cobra, but far less toxic.

The toxins in amorphous and crystalline form are isolated by grinding up dried poison glands with quartz sand, extracting with normal saline, clarifying by aluminium sulphate and precipitating by acetone. The venom is obtained by electrical excitation of the distal coils of the tail.

In South Africa Grasset and colleagues have found neuromotor symptoms follow intravenous injections of the three main genera. Neurotoxins and hæmorrhagins have been isolated from the genus *Parabuthus*. In North-West Africa the danger from scorpions is greater than from venomous snakes.

In the treatment of scorpion-sting in children, it may be necessary to incise and thoroughly wash out the sting with a strong solution of potassium permanganate. Dyce Sharp, from experiences mostly in his own person, advocated immediate injection of an ampoule of novocain and adrenalin in the vicinity of the sting. For the severe intoxications of children, an efficient antitoxin is prepared. The venom extracted from dried stings and venom-glands by normal saline is toxic to horse, goat, and most laboratory animals. The antitoxin has been prepared from horses by subcutaneous injection of graduated doses of venom. In doses of 5 ml. it exerts both prophylactic and curative action. Sargent states that severe symptoms disappear very rapidly after serum injection and when administered early enough and in sufficiently large doses saves many lives. Mortality is less than 3.1 per cent. in all treated cases.

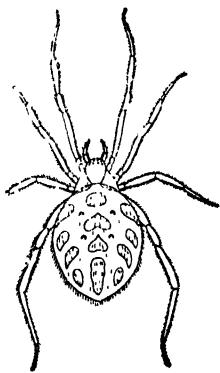


Fig. 244.—Widow Spider (*Latrodectus 13-guttatus*. $\times 2$). (After Hirst, "Journ. Economic Biol.")

Spiders.—Nearly all spiders (*Aranæ*) possess poison-glands, the venom of which is injurious to insects, but few are dangerous to man. Certain of the genus *Latrodectus* are poisonous. In New Zealand one, *L. hasselti*, is known as the "katipo," Maori term for "night-stinger." In Southern Europe, *L. tridecimguttatus*, the "malmignatte" (Fig. 244); in Palestine and North Africa, *L. lugubris* and *L. revivensis*, in North and South America, *L. mactans*, *L. curacaviensis*, and *L. geometricus* are credited with toxic properties.

L. mactans is known in California as the "Black widow spider"; the adult female is glossy black with crimson hourglass markings on the abdomen; in Turkestan *L. tridecimguttatus* is the "Karakurt spider"; in Australia, *Atrax robustus* is "Funnelweb spider" and in South Africa *L. indistinctus* is known as "Kroppie spider" or "button spider."

The toxin of the poison-glands has been shown to be a powerful hæmolysin, causing inflammation and œdema at the site of injection, together with numbness of the part and, it may be, urticarial rash. Most observers describe intense nerve-pain, which is said to be due to stimulation of the myo-neural junctions by the venom. The venom of *L. tridecimguttatus* contains a neurotropic toxin which acts centrally and peripherally. Rigidity and spasm of most of the muscles supervene, especially those of the abdomen, which becomes "board-like," simulating appendicitis. Sloughing of the skin in the neighbourhood of the bite may occur.

Treatment consists in washing out the wound with a solution of potassium permanganate (1 in 4000), and administering it by mouth in doses of one teaspoonful every two hours.

Intravenous injections of calcium gluconate (10 ml. of a 10 per cent. solution)

are said to relieve the pain and decrease the muscular spasm. In South Africa a serum which neutralizes the venom of *L. indistinctus* has been prepared by Finlayson, and similar methods have been used in the Argentine and Russia against local species of *Latrodectus*. Allen advocates *d. tubocurarine chloride* 60 units (9.0 mgm.) given intravenously for relief of pain. It causes immediate relaxation. A.C.T.H. is effective in black widow spider poisoning. When infection occurs penicillin is indicated.

In Peru a prunning spider, *Glyptocranium gasteracanthoides*, which lives in the leaves of vines, and is identified by its ash-grey colour and large globular abdomen with two prominent tubercles, produces, according to Escomel, the same symptoms as *Latrodectus*, and sometimes hæmaturia.

The "tarantula" spider, *Lycosa tarentula* (Fig. 245), occurs in Southern Europe. Mysterious properties have been attributed to its bite; apparently in some specially susceptible people oedema of the eyelids and pyrexia are apt to result, and gave rise to hysterical manifestations known in the Middle Ages as "tarantism." The tarantulas of tropical countries are bird-eating spiders of the family Mygalidæ. They are trap-door spiders, terrestrial in their habits, with prominent projecting mandibles which give them a terrifying appearance. The North African species, *Chetopelma olivacea*, is feared by Arabs, and its bite is said to give rise to acute inflammation.

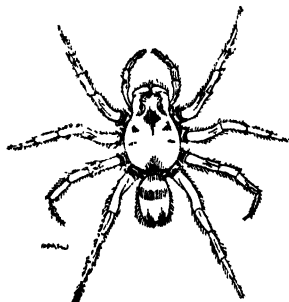


Fig. 245.—Tarantula Spider (*Lycosa tarentula*).
Half nat. size.

Loxosceles laeta ("Araña de los rincones")

Schenone (1959) has reported from Chile a series of 37 patients, mostly women, who were attacked by this arachnid (spider), mostly whilst sleeping or dressing. A gangrenous spot appeared at the site of the bite, mostly on the face, producing periorcular oedema. Rarely hæmoglobinuria results. One patient died.

An antihistamine drug—chloropropen-pyridamine—relieved the local pain and oedema.

CENTIPEDES (MYRIAPODA)

The Chilopoda, to which the poisonous genus *Scolopendra* belongs, are widely distributed in the tropics. They are large creatures, and possess a poison apparatus at the base of the first pair of appendages, which are modified to form jaws. The tropical species, *Scolopendra morsitans*, reaches a large size, up to 6 in.; the venom causes both local and general symptoms. The site of the bite becomes inflamed and the starting-point of lymphangitis; dizziness, headache, and vomiting may ensue.

Treatment consists in bathing the part with a strong solution of ammonia, 1 in 5 or 1 in 10. It may be necessary to give hypodermic injections of morphia to allay pain.

TICK PARALYSIS

Paralysis from bites of *Ixodes pilosus* has long been recognized by sheep-farmers in South Africa. The disease can be reproduced in sheep and guinea-pigs and it has been proved that the virus can be reproduced by the gravid female tick.

Hadwen first found that the tick, *Dermacentor andersoni*, in the dry districts of British Columbia, gave rise in man to a peculiar paralysis which may prove

fatal. This has been reported from North-West States of America and Canada, from the coast of East and West Australia, Cape Colony, Crete, France and Jugoslavia. In America *D. variabilis* is also responsible; in Australia it is *Ixodes holocyclus* and *I. ricinus*; in South Africa *I. pilosus*, *Hæmaphysalis cinnabarina* and *Rhipicephalus simus* (Zumpt). A few days after the attachment of the tick the patient complains of weakness of the legs, then an ascending flaccid paralysis develops, affecting both arms and legs, sometimes with loss of sphincter control. Reflexes are diminished or absent and there may be restlessness and aching of limbs, vertigo, photophobia and vomiting. Signs of bulbar involvement such as respiratory distress, dysphagia and dysarthria may develop suddenly. Death is due to respiratory paralysis. Otherwise the patient recovers completely in 48 hours.

To prevent the onset of paralysis, removal of the tick must be complete, as Clunies Ross and others have shown that the salivary glands are sources of the toxin. A protective serum has been introduced for the treatment of tick paralysis in dogs and has been used successfully in several human cases (Gordon, 1946).

CHAPTER L

MYIASIS AND LEECH INFECTION

NASAL, AURAL, AND OCULAR MYIASIS

The screw-worm fly, *Cochliomyia hominivorax* (Appendix, p. 1074), is common in America. Comparatively often this fly lays its eggs in the nasal and aural cavities, as well as on open sores. The larvæ, known as screw-worms, burrow into the tissues, devouring in their passage mucous membrane, muscle, cartilage, periosteum, and even bone. They may penetrate the brain and cause death. *Callitroga* (*Cochliomyia*) *americana* is attracted to wounds and sores. Epidemics of myiasis due to this fly have been reported in Chile by Tobar and Honorato. In nasal myiasis the initial symptoms are tickling pain and nasal obstruction. Epistaxis is common, but soon the discharge becomes purulent and fœtid. Chloroform inhalations and packing with chloroform gauze are recommended.

Chrysomya bezziana (Appendix, p. 1074), is a true myiasis-producing fly, never breeding in dead, but always in living tissues, in India and Cochin-China. It appears to have a predilection for human beings in India, the female laying her numerous eggs in the nasal cavity or in tissues from which offensive discharges emanate. In the S. Pacific in the 1939-1945 war *Chrysomya megacephala* and *Phormia regina* (a greenbottle) were responsible for traumatic myiasis. A douche composed of 15 per cent. chloroform in light vegetable oil was successful in its eradication.

Rhinæstrus purpureus.—The larvæ of this species are parasitic in the nasal passages of equines in Southern Europe, Asia Minor and Africa, but occasionally the fly attacks man, depositing its eggs in or near the eye, where the larvæ may be seen, moving beneath the conjunctiva, where the destruction they cause may lead to blindness. (See Appendix, p. 1079.)

Wolffahrtia magnifica (Appendix, p. 1074) is the only specific myiasis-producing fly found in man in Europe, but has a wide distribution in Asia Minor and Egypt. *W. vigil* is found in E. and N. America.

Ocular myiasis (ophthalmomyiasis).—In tropical and subtropical countries the larvæ of flies may be deposited on the lids and in the conjunctival sac, whence they may pass into the lacrymal passage, penetrate the conjunctiva and sometimes the sclera, and so gain entrance to the intra-ocular tissues. The species are *Rhinæstrus bovis*, *Hypoderma bovis*, *H. lineata*, *Gasterophilus intestinalis* and *G. equi*. McBride recorded conjunctivitis due to larvæ of the bot-fly (*Æstrus ovis*) in the conjunctival sac.

SUBCUTANEOUS MYIASIS

In South America the "macaw-worm" or "Ver macaque" (p. 1078) (*Dermatobia cyaniventris*) infests cattle, indigenous mammals, and also man.

The eggs are deposited on the skin of human beings, and do not hatch for a day or two. Then the larvæ penetrate the skin, producing an inflammatory tumour, from the aperture of which exudes seropurulent fluid containing black fæces. These have been recorded from various regions of the body, and their presence is usually accompanied by great pain. Busck reported that before they reach maturity the larvæ moult and protrude from the apertures in the skin. In removing them there is no need to use a knife, for the exit aperture may be widened by stretching with forceps; the larva then slips out, aided by properly applied pressure.

In tropical Africa, the tumbu fly, or ver du cayor (*Cordylobia anthropophaga*, p. 1076), produces the same lesions. According to Roubaud, Blacklock, and Thompson, the eggs are first deposited on the ground, and the active young maggot attacks and penetrates the skin of its host, especially on the forearm, scrotum, upper part of the thigh and buttock. The lesion resembles an inflamed

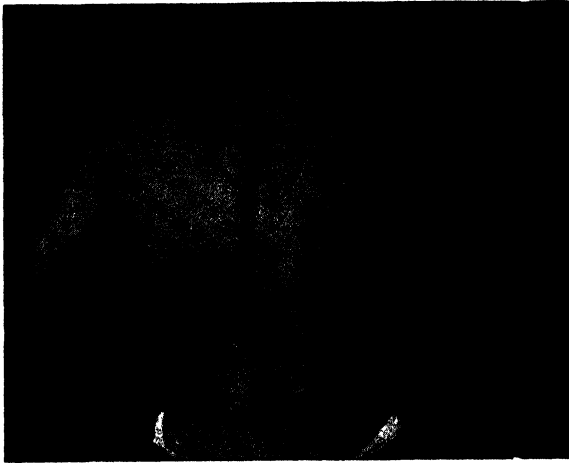


Fig. 246.—Lesions on back caused by *Cordylobia anthropophaga*.
(Orig.)

tumour, from which the larva emerges in six or seven days. These tumours do not usually suppurate (Fig. 246). The fly attacks other mammals besides man.

LARVA MIGRANS

Synonyms.—Myiasis Linearis; Creeping Eruption; Dermatitis Linearis Migrans.

This condition (Fig. 247), first described by Lee in 1874, and at a later period by Crocker, is said to be common in Russia and, according to Kirby-Smith, extremely frequent in Florida. Certainly it is not infrequent in the tropics, especially in Ceylon and South Africa. Here multiple lesions on the legs and feet are produced by a larval nematode burrowing under the skin; this was shown by Kirby-Smith to be that of *Ancylostoma braziliense*, a common parasite of cats and dogs. These observations were confirmed by Fülleborn, who demonstrated that similar lesions may be artificially produced in volunteers by the larvæ of *Ancylostoma stenocephala*, and, to some extent also, by *A. caninum*. Shelmire, Heydon, and Fülleborn in self-inflicted experiments showed that œdema and irritation are considerable. The larvæ of *Gnathostoma spinigerum* and *G. hispidum* have also been incriminated in Thailand (Siam).

Children are mostly attacked between the fingers and toes.

Unlike the itch-mite, the ancylostome larva burrows on indefinitely, like a mole, and forms a red line or narrow raised ridge $\frac{1}{4}$ in. broad. The parasite appears to travel at the rate of $\frac{1}{4}$ –1 in. in twenty-four hours. The line zig-zags and twists about, but does not bifurcate, and may be found in any part of the body—the face, chest, or more particularly the soles of the feet and the legs. While the advancing end of the line progresses, the opposite end fades away (Fig. 248).

The disease may be of very long duration, and is accompanied by intense itching ; sometimes bullæ are formed.

In South Africa, especially in Natal and Zululand, where "creeping eruption" or "sand-worm," as it is called, is very common, Murray (1939), by aid of cedarwood oil technique, proved that sometimes the burrows are produced by a mite, possibly related to *Tetranychus molestissimus*, which is found in Argentina and Uruguay, attacking man and animals. The tracks in the skin are 0.33 mm. in diameter. The mite, and its eggs, are easily demonstrated at the end of the burrow. A drop of distilled water on a clean slide prepared with Mayer's egg albumin facilitates this procedure.

It is possible, as Fülleborn and da Rocha-Lima suggested, that the tropical form differs from that described in Russia and America. The former appears to be due to the burrowing under the epidermis of fly larvæ which have been identified as those of *Hypoderma*, *Gasterophilus hæmorrhoidalis*, and *G. veterinus*.



Fig. 247.—Larva migrans 4 months after probable infection at Durban.
(Philip Manson-Baehr.)

The lesions of the ancylostome larvæ group can be distinguished from those of *Gasterophilus* by being shorter and more complex.

Austmann used Lombard's method of clearing living skin to demonstrate larvæ of *Gasterophilus* in cases produced by this insect. Ordinary machine-oil is used and the epidermis cleared around the line of creep. Using the binocular dissecting microscope, the parasite may be seen lying between the cornified and granular layers of the epidermis. With a magnification of 150 diameters, details of structure can be clearly seen.

In Florida creeping eruption has a definite seasonal prevalence during the summer months, after periods of rainy weather. Most cases originate on the beach above high water mark. There is some evidence that it is connected with sewage disposal. Dogs and cats are the hosts of the adult *A. braziliense*.

Treatment.—Excision of the portion of the burrow containing the advancing larva may be attempted, though refrigeration with ethyl chloride has been found effective. An area of one and a half inches at the visible end of the burrow should be frozen for two to four minutes. The spray should be directed about half to

one inch in front of the inflamed end of the burrow. If the burrows are multiple, it should only be applied to a few at a time. Arthur and Shelley (1958) found that injection of *lyophilized trypsin* into the burrow is effective.

Bayley (1941) claimed that the most scientific treatment consists of locating the larva by means of the cedarwood oil method, then injecting 1 in 1000 procaine in order to desensitize an area of over half an inch in diameter with the larva in the centre. A cauterizer is then applied until a small burn is produced. Sulphonamide, 0.5 gm. for two days, helps to heal and prevents secondary infection. Each burrow must be examined in turn. According to Kelsey, refractory cases are best treated by diathermy, using the needle point of the apparatus with a $\frac{1}{8}$ in. spark. Intradermal injection of 30 per cent. N/methylglucamine antimonial (*Glucantime*), 1 ml., into each site affected at the end of the canal every

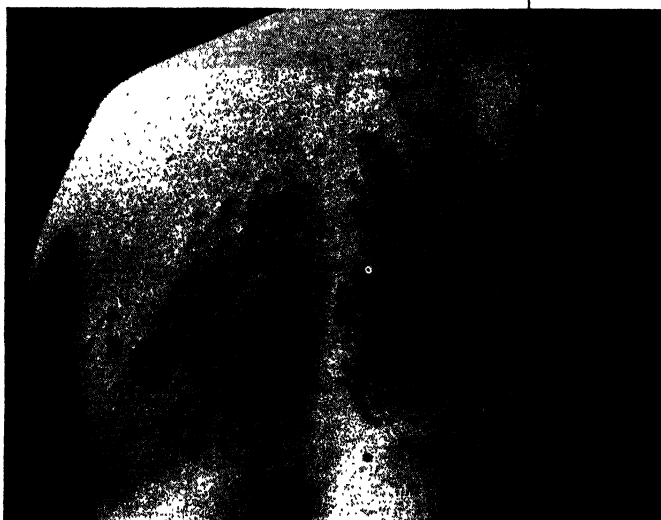


Fig. 248.—Multiple burrows of larva migrans, from Ghana. (Orig.)

fourth day is recommended by Gambini. Loewenthal (1950), in treatment in S. Africa, recommends hetrazan in doses of 2 mgm. per kg. thrice daily and this has been found to be particularly successful. The natural duration of this disease is about four months. By this method it is reduced from 13–28 days. Improvement was rapid in 2–17 days. Control measures consist of excluding dogs and cats from the beaches, restricting bathers to that part washed by the tide, wearing shoes, and treating dogs and cats with tetrachlorethylene to remove adult worms.

Visceral larva migrans (Welder, 1950; Beaver *et al*, 1952; Heiner and Kery, 1956). This syndrome is being recognized with increasing frequency at Massachusetts General Hospital and is attributed to the ingestion of embryonated eggs of the round worm, *Toxocaria canis* of the dog, *T. mystax* of the cat and to subsequent migration of the larvæ in the viscera. Splenomegaly is common, while pulmonary infiltration leads to respiratory distress with wheezing and may prove fatal. Various kinds of urticarial rashes may occur. Convulsions have

been recorded, also pseudotumour of eyes. Diagnosis is assisted by leucocytosis of 12,000 to 100,000 and eosinophilia of 15–80 per cent.¹ Hyperglobinæmia is present with increase of gamma globulins (see Tropical Eosinophilia, p. 686). Fertile ascaris eggs are found in the soil, or in basement dust of the patients' homes.

BLOODSUCKING LARVÆ

Auchmeromyia luteola (Appendix, p. 1077), the larva of which is commonly known throughout the Congo as the "floor maggot," has a wide distribution throughout tropical Africa, from Northern Nigeria to Natal. The adult fly is usually found among the thatch and beams of the walls and roofs of native huts, and deposits its eggs in crevices of the mud floors. Here the larvæ hatch and move about in the moist earth. They emerge from their hiding-places to feed mainly at night.

Sucking of blood is effected in a curious manner; the head segment is retracted, and the lips of the second form a sucking disc attaching the larva to the skin of its host; the skin is scarified by curved hooks, and thus blood is drawn. The larva soon assumes a red colour due to absorbed blood. It is said that the bite is non-irritating.

INTESTINAL AND URINARY MYIASIS

Residence in the alimentary canal of some vertebrate animal is a regular feature in the life-history of many dipterous insects. The eggs are either licked from the skin or swallowed in the food on which they have been deposited. In this way they are transferred to the stomach, where, after an interval, the larvæ are hatched out and undergo development. In due course they appear in the fæces. Man is not infrequently victimized, especially in tropical countries. Sometimes, until a correct diagnosis is arrived at, not a little alarm is caused by the appearance of these creatures in the stools or vomit. They are easily recognized. The ringed, cylindrical body, $\frac{1}{2}$ –1 in. in length, according to species, broad at one end, tapering at the other, and usually beset with little spines or hairs, is sufficiently diagnostic (Fig. 249).

Already over twenty species of diptera are recognized whose larvæ have been found in or expelled from the intestinal canal. The commonest form is *Calliphora vomitoria*.



Fig. 249.—Larva of *Calliphora vomitoria*.

In Europe the majority of cases of intestinal myiasis, a not infrequent occurrence, are caused by *Fannia canicularis* and *F. scalaris* (flies closely resembling the common housefly, and erroneously considered a young form of the latter on account of its smaller size). Occasionally, pains in the abdomen, vomiting, and diarrhœa may ensue, and there may be evidences of toxic absorption; more usually these occur when the ingested larvæ are those of the cheese maggot, *Piophilæ casei*. Larvæ of the common housefly (*Musca domestica*) have been found in numbers in the stomach in the Philippines. In Africa the insect commonly found is *Chrysomya chloropyga*, and occasionally *C. putoria*.

¹Yung and Pacheco (1960) have devised a hemagglutination test, using tanned sheep's corpuscles to test patients suspected of visceral larva migrans and found 79.3 per cent. positive for *Toxascaris canis* and for *Ascaris* spp.

A dose of castor oil will probably suffice to expel any of these creatures that may not have been passed spontaneously.

Rational prophylaxis consists in covering up food after it has been cooked, in order to prevent the access of flies.

Instances in which larvæ of *F. canicularis* and *F. scalaris* have been discharged *per urethram* have also been met with, though more rarely.

LEECH INFECTION

In the grass and jungle lands of many tropical and subtropical countries land-leeches, probably of special species, often occur in great abundance; so much so that in some circumstances they may prove more than a nuisance. *Hæmadipsa zeylanica* in Ceylon is one of the most active, as well as best known. Leeches have a sucker at each end. They can either swim or loop along, aided by their suckers. The crop has numerous off-shoots, in which the sucked blood can be stored, so that the leech can do without another meal for some considerable time. The blood is prevented from clotting by the secretion of an anticoagulant. Before feeding, when outstretched, it is about an inch in length and about the thickness of a knitting needle. It clings to a leaf or twig, awaiting the passing of some animal, on to which it springs with remarkable activity. It can insinuate itself through the meshes of the finest stockings. It at once attaches itself to the skin and proceeds to make a meal of blood. Animals are sometimes killed; men even have been known to succumb to repeated small bleedings by these pests. It is necessary, therefore, when passing through jungle lands in which leeches abound, to have the feet and legs carefully protected. The bite is not infrequently the starting-point of a troublesome sore. Leeches abound in Malaya, and in Ceylon. After rain a traveller in the jungle is likely to find his boots full of blood. *H. japonica*, in Japan, Philippines, Indonesia and S.W. Africa, generally, has similar habits.

In the south of Europe and in the north of Africa the horse-leech, *Limnatis nilotica* (Fig. 250), which lives in ponds and other collections of water, sometimes



Fig. 250.—*Limnatis nilotica*. Half nat. size. (Sheppard, del.)

finds its way into the gullet and nostrils; and has occasionally caused death by entering and occluding the air-passages. These leeches are a source of inconvenience to French troops in Algeria, and are mentioned as troubling Napoleon's army in its retreat through Sinai; several cases were noted among British troops during the Egyptian and Palestine campaigns in 1914–1918 and again in 1939–1945 wars (Reeves). In Formosa, Patrick Manson heard of and saw several instances of a similar form of parasitism, both in men and in monkeys. The species here were immature examples of *Dinobdella ferox*.

Doubtless, when very young the leeches are taken in unperceived with foul drinking-water, and, wandering round the soft palate, find their way into the nose. For a long time they contrive to elude all attempts at capture, but can generally be persuaded to show themselves by dipping the face in cold water. An American naturalist, who had been travelling much in the interior of Formosa, had suffered from severe headache and profound anæmia, the results of repeated epistaxis. Manson succeeded in removing a leech by attaching to its hinder end, through a speculum, a spring forceps, and afterwards injecting salt and

water. Therefore in tropical countries persistent headache, associated with recurring epistaxis, may be caused by a leech in the nostril. Travellers in leech-infested countries must wear knee-length, waterproof leather boots and khaki pants and should liberally apply repellents, dimethyl phthalate, or indalone, to all clothing liable to infestation. Ribbands (1946) found that 4 ml. per sq. foot of clothing protects for 21 days and it must be applied thoroughly to the inside of boots and socks.

In Java *H. javanica* occurs. Other species are *H. fallax* from Madagascar. Others such as *H. morsitans* and *H. vagans* constitute a scourge in Sumatra, New Guinea, Celebes, Borneo, French Indo-China, Chile and Trinidad. The land leech of S. Australia belongs to the genus, *Philæmon*.

Section XI.—SPECIAL SUBJECTS

CHAPTER LI

BLOOD GROUPING AND TRANSFUSION

THE BLOOD

IN addition to the morphological changes in the red and white corpuscles (*see* p. 1094) there are the physiochemical changes which present a basis for investigation when the body is considered as a physiological unit.

Total Blood Volume.—It is desirable that it should be possible to measure this as it underlies the meaning of all other blood investigations.

The normal value of whole blood is 6 to 9 per cent. of body weight. The total blood volume varies from:

65–80 ml./kgm. body weight: 3·5–7 litres or 6–12 pints and 2,500–8,200 ml./sq. metre of body surface. On the whole the figures are 7 per cent. higher in men than in women.

Normal volume of plasma:

4·8 to 5·7 per cent. of body weight.

43–57 ml. per kg. body weight.

2–4 litres or 3·5 to 7 pints.

Most methods of determining blood volume in use are based on the principle that, by the addition of a definite quantity of a known substance to the circulation, the total quantity of blood may be calculated from the concentration of the foreign substance in the sample of blood.

All these tests measure either the corpuscular volume or the plasma volume, and the total blood volume is calculated from this by means of the hæmatocrit values.

Amongst the substances used are carbon monoxide, radioactive phosphorus, radioactive chromium and radioactive iron. For the determination of plasma volume the dyes, Evans blue, neutral red, or radio-active iodine are used. The total blood volume is *raised* in polycythæmia and in overtransfusion of blood. It is lowered by severe blood loss, and hypoproteinæmia.

Whole Blood Specific Gravity.—In normal man it is 1055–1060, and in native Indians 1054; usually it is lower in women and in newborn infants. It is raised in conditions of reduced plasma volume, such as acute diarrhœa, bacillary dysentery and cholera. In the acute stage of the latter it usually varies between 1,060 and 1,068, reaching sometimes as high as 1,076, a figure which expresses the loss of nearly half the fluid from the blood and indicating transfusion of saline.

Bleeding time is 2–7 minutes. This is raised in idiopathic thrombocytopenia, and also in hæmorrhagic thrombocytopenia (onyalai),

occasionally also it is raised as a complication in overdosage with iodides, salicylates, atropine and thiouracil.

Blood Platelets.—Normal 200,000–600,000 cmm.

Raised after exercise, splenectomy, rheumatic fever, hæmorrhagic thrombocytopenia (onyalai). After any acute illness, with sickle-cell anæmia, also in Hodgkins' disease, chronic myeloid leukæmia, and in iron deficiency.

Lowered in primary aplastic anæmia, acquired hæmolytic anæmias, including nocturnal paroxysmal hæmoglobinuria, in cirrhosis of the liver, kala-azar, pernicious anæmia, scurvy, leptospiroses. Also by certain drugs, such as carbamides (sedormid), barbiturates, pyrazolon derivatives, quinine, quinidine, sulphonamides, organic arsenicals, para-aminosalicylic acid (PAS), digitoxin, DDT, butazolidin, isonicotinic acid hydrazide (INAH).

Prothrombin time.—Coagulation is up to 20 seconds, if the normal control is 12 seconds, but more than 30 seconds denotes lowered prothrombin concentration. Circulating prothrombin deficiency is found in obstructive jaundice, biliary fistula and steatorrhœa (tropical sprue). Also in intestinal obstruction, intestinal fistula, chronic pancreatitis, ulcerative colitis, prolonged antibiotic therapy, any form of acute or chronic liver disease and circulating anticoagulants with dicoumarol or heparin and in yellow fever.

Hæmoglobin (Hb).—(All figures are in grm./100 ml.). The normal values are:

Normal hæmoglobin: *men* 16.0 ± 2.0 (grm.)

(94–120 per cent. Haldane's method)

women 14.0 ± 2.0 (grm)

(81–108 per cent. Haldane's method)

children

At birth: 14.5–24.5, falling rapidly to approximately 12.0 at 6 months.

One year 11.2 : 2 years 11.5 : 3 years 12.5 : 10 years 12.9 : 14 years 13.4 grm.

Values are raised in primary polycythæmia, chronic anoxæmia (emphysema, congenital heart disease).

Values are lowered in simple deficiencies, iron deficiency, vitamin B₁₂ deficiency (pernicious and other megaloblastic anæmias) (*see* p. 20) also in vitamin-C deficiency, scurvy and secondary to blood loss or blood destruction.

A. Hæmolysis: Hæmolytic anæmias such as spherocytosis (acholuric jaundice), sickle-cell anæmia, hæmoglobin C disease, thalassæmia, septicæmia, hæmolysis due to drugs—e.g., lead and phenylhydrazine, also in chronic malaria, Oroya fever (p. 206).

B. Blood loss: Peptic ulcer, carcinoma of stomach or colon, menorrhagia, extensive purpura.

C. Mixed or undeterminate origin: Leukæmia, uræmia, chronic infections, such as histoplasmosis, kala-azar, pulmonary tuberculosis, trichiniasis, osteomyelitis.

Primary steatorrhœa (tropical sprue), chronic liver disease (amœbic abscess), parasitic disease.

Diphyllobothrium and hookworm infections (*see* p. 790), myxœdema, hyperthyroidism.

Abnormal compounds of hæmoglobin.

Methæmoglobin is normally present in almost 2 per cent. of hæmoglobin. Percentage is increased in intravascular hæmolysis, poisoning and idiosyncrasy to drugs, such as sulphonamides, phenacetin, sulphonal, potassium chlorate, pamaquine (*see* p. 78), primaquine (*see* p. 78), nitrobenzene, isoniazid (INAH). Idiopathic and familial methæmoglobinæmia recognized.

Methæmalbumin (*see* p. 58) is a combination of serum albumin with methæmoglobin found in serum in blackwater fever and some severe hæmolytic fevers.

Packed Cell Volume (P.C.V.).—

Men 47 ± 7 per cent.

Women 42 ± 5 per cent.

Children in proportion to hæmoglobin changes already mentioned.

Raised in polycythæmia and reduced plasma volume (in the absence of anæmia and blood loss).

Lowered in normocytic and macrocytic anæmias and most of anæmias mentioned under *hæmoglobin*, except iron deficiency; more so in microcytic than in macrocytic types.

Red Blood Cells (Total R.B.C's).—

Men 5.4 ± 0.8 (millions per cmm.).

Women 4.8 ± 0.6 .

Children

At birth: 5.1 ± 1.0 falling to approximately 4.6 in 6 months.

Constant during childhood.

Approximately 4.8 at the age of 14 years.

Raised in polycythæmia and thalassæmia minor (p. 29).

Lowered in most types of anæmias.

Time and energy are wasted in performing unnecessary red blood counts, unless in very experienced hands the count is inaccurate as a means of measurement and the indices derived from it (C.I., M.C.H. and M.C.V.) become correspondingly so. The hæmoglobin value and the morphology of the red cells constitute a much more reliable and accurate guide.

Red cell dimensions.—(a) *Mean cell diameter* (M.C.D.) $7.5 \pm 0.3 \mu$ is the same for men, women and children over 10.

At birth: 8.6μ falling slowly to 7.4μ at six months, 7.3μ at one year gradually rising to 7.5μ at 10 years. (All normal values are for dried fixed films. Living cells of adults average 8.8μ in diameter.)

Raised in pernicious anæmia, megaloblastic anæmias, chronic liver disease, primary steatorrhœa (sprue), thalassæmia (*see* p. 29), anæmia of malignancy and of many chronic diseases, myxœdema and hyperthyroidism.

Lowered in iron deficiency, congenital spherocytosis (familial acholuric jaundice), simple achlorhydria.

Red cell indices.

(a) *Colour Index.*

C.I. 1 ± 0.1

Hb% $\times 5 \times 10^6$ mill./cm.

RBC's $\times 100$

Children

Very high at birth, falling slowly to 0.85 (lowest) at 1 year. Rises slowly to adult values.

A *high colour index* suggests macrocytic anæmia, especially pernicious and other forms of megaloblastic anæmia as well and also tropical sprue. But a normal colour index does not always exclude macrocytic anæmia. A low colour index is found in microcytic anæmia, particularly iron deficient anæmia and thalassæmia.

(b) *Mean corpuscular hæmoglobin (M.C.H.).*

Hb (gm.)/100 m. $\times 10$

RBC's (mill./cmm.)

Normal Value

$29 \pm 2 \mu\text{g.}$

Children.

88 μg at birth falling slowly to 25 μg (lowest) at 1 year, then rising slowly to adult values).

(M.C.H. is another method of expressing the colour index without recourse to the Haldane hæmoglobin percentage scale, but a red blood count is necessary.)

(c) *Mean corpuscular hæmoglobin concentration (M.C.H.C.).*

Normal values (same in men and women) 34 ± 2 per cent.

Hb (gm./100 ml.) $\times 100$

P.C.V. (%)

(Packed cell volume)

36 per cent. at birth, falling slowly to 32 per cent. (lowest) at 1 year. Rises slowly to adult values.

Raised in pernicious anæmia and some other anæmias without associated iron deficiency.

Lowered in iron deficiency anæmia. Values < 32 per cent. suggestive and < 30 per cent. diagnostic of iron deficiency, provided that thalassæmia and polycythæmia are not present. Thalassæmia, primary polycythæmia, hæmoglobin E disease or hæmoglobin H disease (see section on hæmoglobinopathies (p. 22)). M.C.H.C. is an accurate measurement of the average hæmoglobinization of the red cell.

(d) *Mean cell volume (M.C.V.).* Normal values $87 \pm 5 \mu$

P.C.V. (%) $\times 10$

RBC (mill./cmm.)

Raised in macrocytic anæmias with marked reticulocytosis, congenital spherocytosis (acholuric jaundice).

Lowered in thalassæmia, iron deficient anæmia, and liver disease.

Children 106 μ at birth, falls to 78 μ at one year, then rises slowly to adult values.

Red cell sedimentation (ESR or BSR).

Normal values. *Men*: 0–9 mm.

Women: 0–14 mm.

At one hour (Wintrob's method).

Men: 3–5 at 1 hour; 15 mm. at 2 hours.

Women: 4–7 at 1 hour; 12–17 mm. at 2 hours. (Westergren's method.)

Raised in many general diseases, febrile states especially tuberculosis, trypanosomiasis, especially *T. rhodesiense*, pregnancy, myxœdema. Useful in assessing results of treatment.

Lowered in congestive heart failure, severe liver disease, polycythæmia, sickle-cell anæmia.

(It is doubtful whether allowance should not be made for anæmia. It must be remembered that a normal sedimentation rate cannot exclude serious disease.)

Sedimentation rate of red corpuscles.—Any increase of the rates of fibrinogen and serum globulin to that of serum albumin leads to an increased rate of sinking of the red blood corpuscles. The increase of the rates may be due to an actual increase of fibrogen, serum globulin or even both, or to a reduction in serum albumin. The rate of sinking is also increased when the number of red blood corpuscles is reduced. The rate of sedimentation is increased by the height of the column of plasma left clear in a given time by the sinking of the red blood corpuscles.

White cells (total WBC's).

Normal values 4,000–11,000/cmm. (Highest in morning and late evening.)

Raised in many conditions (see p. 1095), bacillary dysentery, cholera, amœbic hepatitis, amœbic abscess of liver, relapsing fevers.

Lowered (leucopenia) in aplastic anæmia, aleukæmic, leukæmia, pernicious anæmia, iron deficient anæmia, portal vein thrombosis, cirrhosis of the liver, kala-azar, typhoid, brucellosis, miliary tuberculosis, swine herds' disease (*Leptospira pomona*), infective hepatitis, influenza, measles, rubella, dengue, phlebotomus fever (p. 336). To a lesser extent in malaria, histoplasmosis, trypanosomiasis, lupus erythematosus, after some antibiotics, especially chloramphenicol, some drugs such as mercurial diuretics, phenylbutazone, gold, arsenic and amidopyrine.

BLOOD CHEMISTRY

Bilirubin.—Normal values—0.1–1.0 mgm./100 ml. (Direct reaction is usually negative. Serum bilirubin measures the "indirect" reacting bilirubin in the Van den Bergh reaction. Only the "direct" reacting form is normally excreted in the urine. This reaction is positive in conditions in which bilirubin has been secreted by the liver and then partly reabsorbed into the blood. It is found most commonly in *obstructive jaundice*.)

Rises at birth to maximum of 11 mgm./100 ml. at 4th day; then slowly falls.

Raised in hæmolytic jaundice: yellow fever reaches maximum on the 6th day. Congenital spherocytosis (familial acholuric jaundice), sickle-cell anæmia, thalassæmia, pernicious anæmia, paroxysmal nocturnal hæmoglobinuria, paroxysmal cold hæmoglobinuria, incompatible transfusion, erythroblastosis foetalis, lead, quinine, phenylhydrazine, hydrogen sulphide, acetanilide; sulphonamides, urethane poisoning; favism, septicæmias, gas gangrene, malaria, Oroya fever, virus pneumonia, extensive burns, infective hepatitis, homologous serum hepatitis, yellow fever, leptospirosis, glandular fever; sometimes with arsenic, chloroform, carbon tetrachloride and phosphorus poisoning. Cirrhosis of liver, congestive heart failure, obstructive jaundice, gallstones, carcinoma of head of pancreas, cholangitis, cysts of liver; parasites such as *Clonorchis sinensis* or *Fasciola hepatica* in bile ducts.

Calcium.—

Normal values: 9.6–10.9 mgm./100 ml. (4.8–5.4 m. Eq. Ca/litre).
(4.25–5.25 mgm. ionized, Ca^{++} /100 ml).

Raised in hyperparathyroidism, hyperproteinæmia, Vitamin D intoxication, idiopathic hypercalcæmia of infants, sarcoidosis, excessive milk and alkali treatment in peptic ulcer. Malignant disease of bone, lymphoma, leukemia, polycythæmia, cholera.

Lowered in total parathyroidectomy, idiopathic hypothyroidism, chronic renal failure, hypoproteinæmia, primary steatorrhœa, tropical sprue, acute pancreatitis, osteomalacia and occasionally in rickets.

Proteins.—Total 6–8 gm./100 ml. Slightly less in infants.

Raised in conditions with very high serum globulins, without low serum albumin, such as kala-azar, malaria, trypanosomiasis, leprosy, undulant fevers, early stages of infective hepatitis, conditions with reduced plasma volume without loss of protein, as in acute cholera.

Lowered in low serum protein values—and due to low serum albumin concentration—such as epidemic dropsy, cardiac beriberi, malnutrition, especially kwashiorkor.

Albumin.—Total 4.0–5.5 gm./100 ml.

Raised in hæmoconcentration, as in cholera.

Lowered in inadequate intake of protein, starvation, kwashiorkor (malnutrition), advanced carcinoma, chronic pulmonary tuberculosis, primary steatorrhœa (sprue), cardiac beriberi, epidemic dropsy, leprosy, trypanosomiasis (especially *T. rhodesiense*), chronic pancreatitis, acute necrosis of liver, hyperthyroidism. *Loss of albumin* in urine, nephrosis and nephritis, extensive burns, ascites.

Globulin.—Total 2.0–3.5 gm./100 ml.

Raised in myeloma, liver disease, kwashiorkor, infective hepatitis, cirrhosis, nephrosis, pneumonia, subacute bacterial endocarditis, tuberculosis, leprosy (mainly α and γ , especially in lepra reaction), lymphogranuloma venereum, typhus, kala-azar, cardiac beriberi, undulant fevers, ancylostomiasis (γ globulin), trypanosomiasis (*T. rhodesiense*, Woodruff), malaria, (γ globulin), syphilis, schistosomiasis, histoplasmosis, filariasis

(mainly γ in *W. bancrofti*), rheumatic fever, rheumatoid arthritis, periarteritis nodosa, lupus erythematosus, cardiac infarction, carcinomatosis, leukæmia, acute cholera, extensive burns.

Lowered in starvation, steatorrhœa (sprue) and epidemic dropsy.

Hapta Globins (Allison, 1958) are members of the α_2 and β group of globulins. Their development is under genetic control and an individual may possess 1, 2 or 4 (or more) with slightly differing electrophoretic mobilities. Their function is to take up and to carry free hæmoglobin molecules in the circulation.

Urea.—Normal values 16–35 mgm./100 ml.

9–17 mgm. nitrogen/100 ml.

Raised in primary renal diseases such as acute and chronic glomerulonephritis, chronic bilateral pyelonephritis, advanced bilateral renal tuberculosis, advanced nephrosclerosis, chronic gout, "crush syndrome," acute cholera, leptospirosis, periarteritis nodosa, amyloidosis, hæmoglobinuria, mainly in incompatible transfusion. Chronic hypercalcæmia or hyperparathyroidism, yellow fever, prostatic hypertrophy, cirrhosis and chronic liver disease.

Lowered in acute hepatic necrosis in virus hepatitis, eclampsia, poisoning by arsenic, carbon tetrachloride, chloroform and phosphorus.

Uric Acid (blood).—Normal values 1.6–3.6 mgm./100 ml.

Raised in gout (a high level is suggestive, but not conclusive evidence of gout). Conditions associated with excessive breakdown of cell nuclei, primary polycythæmia, malignant lymphoma, hæmolytic anæmias, chronic myeloid leukæmia, lead and mercury poisoning.

Lowered in administration of aspirin and atophan, functional hyperinulism, islet cell tumour, primary steatorrhœa (sprue), hypopituitarism, glycogen storage disease (von Gierke); sometimes in cholera.

Phosphatases.—

Acid: Normal values 1.2–3.1 units/100 ml.

Raised in metastatic carcinoma of the prostate (following with hormonal treatment) osteogenesis imperfecta, osteoporosis, hyperparathyroidism.

Alkaline: Normal values 4.5–12 units/100 ml.

(Low at birth, but rises rapidly up to 5 times normal levels at one month; declines slowly during childhood.)

Raised in Paget's disease, hyperparathyroidism, biliary cirrhosis, obstructive jaundice, carcinomatosis of liver, rickets, osteomalacia, renal rickets, osteogenic sarcoma, infective hepatitis, cirrhosis of liver.

Lowered in hypophosphatasia (bone disease simulating rickets) senility, malnutrition.

Potassium.—Normal values: 15.1–19.6 mgm./100 ml.

3.9–5.0 mEq./litre.

Raised in too rapid parenteral administration of potassium solutions, especially those patients with dehydration or renal disease, severe chronic renal failure, vigorous muscular exercise, Addison's disease, cholera (severe).

Lowered in chronic severe diarrhœas, tropical sprue and idiopathic

steatorrhea, intestinal fistulae, prolonged postoperative gastric aspiration, excessive loss of potassium by the kidneys in heat stroke, Cushing's syndrome, renal tubular acidosis, after a large meal (associated with storage of glycogen), malignant malnutrition (kwashiorkor). In cholera during treatment with intravenous salines, rehydration of patients with diabetic ketosis, recovering renal tubular necrosis.

BLOOD GROUPING AND BLOOD TRANSFUSION

Before a patient is given a blood transfusion the blood of the donor and that of the recipient must be carefully grouped and cross-matched. Under modern conditions the blood must be grouped both in the ABO system and the Rhesus-Rh system. Only compatible blood may be used for transfusion and it is essential that no blood must be issued without first carrying out the necessary tests. The blood grouping, Rh typing and compatibility tests should be performed by doctors and technicians who have some previous experience and training in this subject.

A.B.O. Grouping Tests.

Slide method of blood grouping.—Prepare a 1 : 20 dilution of the donors' blood in normal saline, using a white cell diluting pipette. On a slightly warmed microscope slide, mark two circles with a grease-pencil, marking one A, the other B. Then place a drop of anti-B. serum in the B circle, and a similar drop of anti-A. serum in the A circle and add a drop of red cell suspension of the 1 : 20 dilution of sample to each drop of serum, great care being taken so as not to contaminate the pipette with the serum. Rock the slide so as to mix the sera and the cells, cover it with a Petri dish, leave for 10 minutes and then examine for agglutination. The examination should be repeated after a further 10 minutes, when *haemolysis* should not have occurred and the granular appearance of the agglutinates should become readily visible. When the naked eye appearances are doubtful, the true agglutination (differentiation from rouleaux formation) should become obvious.

The recipients' serum should also be grouped by utilizing known group A and group B suspensions in a 1 : 20 dilution in normal saline. Then a check on the recipients' group is made.

Results in A.B.O. Grouping Tests.

CIRCLE A ANTI-A SERUM	CIRCLE B ANTI-B SERUM	BLOOD GROUP
Agglutination	Agglutination	AB
Agglutination	—	A
—	Agglutination	B

The tube method of blood grouping is perhaps slightly more sensitive than the slide method, but takes longer to perform.

Rh. typing tests.—Place 2 drops of anti-Rh. serum in a small precipitin tube with an internal diameter of about $\frac{1}{8}$ in., add 2 drops of 20–30 per cent. bovine albumin and 1 drop of a 15 per cent. suspension of red cells in normal saline. The serum and cells are mixed by sharply flicking the tube with the index finger. The tube, together with *control* tubes containing (I) Rh.-positive cells, (II) Rh.-negative cells, and (III) normal saline, are incubated for up to 2 hours at 37° C.

Examine the red cell sediment with a hand lens at the end of 30 minutes and, if agglutination has occurred, the cells are Rh. positive, and the test should be considered conclusive. If, however, the result is still negative the incubation should be continued up to 2 hours. The sediment of agglutinated erythrocytes has a peculiar, characteristic, wrinkled appearance, while the sediment of unagglutinated cells is circular and smooth.

Coombs' test.—This is a very sensitive test and a very useful one for detecting antibodies *adsorbed* on the surface of the red cells. Coombs' serum is an anti-human globulin serum prepared by immunizing rabbits. This test is of value for detecting rhesus sensitization and for demonstrating adsorbed antibodies as in the case of certain *hemolytic anemias*.

The Coombs' test may be used as an adjuvant to the usual grouping method when agglutination is doubtful.

For this test the blood should be kept in a refrigerator. False negatives may occur if the blood is left for more than 1 hour at room temperature since the antibodies may leave the surface of the cell.

Direct test.—Use 2 drops of the patients' blood, or of the sedimented cells from a clotted specimen. Dilute with normal saline to about 5 ml. and centrifuge at 3,000 r.p.m. for 2 or 3 minutes. Discard the supernatant liquid and repeat the washing twice. The thrice-washed cells are then diluted to 2.5 ml. with normal saline, making approximately a 5 per cent. suspension of cells in saline, but if the reaction is a weak one, it should be diluted to 1 ml. only. Great care must be taken of the washing stage because even a faint trace of serum will give false positive results.

A tube of frozen anti-human globulin serum for Coombs' test is taken from the deep-freeze section of the refrigerator and the contents warmed to 37° C. The serum is then diluted with normal saline according to the instructions on the label and it should be used immediately, but once it has been reconstituted the serum quickly deteriorates and should not be stored again for future use.

Two drops of the reconstituted serum on a tile are warmed to 37° C. and one drop of the patients' cell suspension is added. The drops should be mixed with a wooden applicator stick and the tile rocked. At the same time control tests must be carried out, using in place of the patients' cell suspension, (I) group O rhesus-positive cells with incomplete anti-D serum which has been incubated for 1½ hours, washed 3 times in normal saline, and then stored at 4° C, and (II) with group O rhesus-negative cells alone. A positive reaction is visible to the naked eye, usually within 2 minutes. A negative report should not be given until after 10 minutes at the end of which the tile should be rocked for 30–60 seconds.

Indirect test.—In this test the presence of rhesus *antibodies* in the patients' serum is shown. The technique is too complicated for practical use in small laboratories.

Direct cross-matching test.—Before giving any blood transfusion it is essential to ascertain that the donors' red blood corpuscles are compatible with the recipients' serum and therefore direct cross-matching must be carried out between the patients' serum and every sample of blood issued for transfusion.

Then, if more than one bottle of blood is required, the cross-match test must be repeated for each bottle used. Compatibility should also be demonstrated between donors' serum and recipients' red cells in cases of grave anæmia when applying the blood transfusion, 2 ml. of a fresh sample of the prospective recipients' blood should be submitted to the laboratory, since irregular antibodies may be formed in the recipients' serum after one or more transfusions. Therefore further samples of the recipients' blood should be cross-matched each time a new transfusion is contemplated.

Slide method.—From the pilot tube attached to the neck of the transfusion bottle, remove a drop of whole blood and make a fresh cell suspension by mixing with sufficient normal saline to make 2 ml. Mix one drop of this donors' cell suspension in a slide; place in incubator at 37° C., keeping moist by placing a moist plug of cotton wool in the vicinity and cover with a Petri dish for another 10 minutes and re-examine. Exposure to draughts of cold air should be avoided in case the patients' serum contain non-specific cold agglutinins which may cause a false reading. Bacterial contamination also may invalidate this test.

THE RHESUS FACTOR

The third source of agglutinating serum, a Rhesus antibody, for the first time linked blood groups with real disease. It had long been known that mothers who had had one or more normal pregnancies might suddenly produce a child suffering from hæmolytic anæmia and jaundice at, or soon after birth. In the serum of these mothers the Rhesus antibody could frequently be demonstrated, both before and after birth, or again they were Rhesus-negative. It therefore became necessary to extend Rhesus grouping to all pregnant mothers and to test all who were found to be Rhesus-negative for the possible presence of antibody before they came to term. Those likely to be affected were selected and made it possible to carry out tests on the cord blood at birth, to be followed by immediate exchange transfusion if necessary.

The Rhesus antibody, forms in the Rhesus-positive blood, however small the quantity may be. That the antibody does not always develop may be explained by differences in the relative sensitivity of individual patients. Mothers then become exposed by escape into the circulation of small quantities of blood from her unborn child. In succeeding pregnancies the antibody increases in strength and may affect the child. The child inherits its Rhesus-positive factor from its father. If the father was Rhesus-negative, then no immunization would occur and the child would be perfectly normal. The Rhesus antibody formed in the serum of the

mothers' blood, to destroy Rhesus-positive cells, passes through the placenta and then encounters large numbers of these cells in the body of the foetus. The process of destruction is then initiated and is known as *Erythroblastosis foetalis* or "Hæmolytic Disease of the Newborn," marked by anæmia, jaundice, petechial hæmorrhages, spleno- and hepato-megaly. Death may occur within three days. The only method of treatment involves the removal after birth of as much as possible of the affected blood of the child by exchange transfusion with unaffected blood from a normal donor.

Transfusion technique.—In giving transfusions two points require special attention. Firstly, in chronic anæmic and diseased subjects transfusions must be given very slowly, such as a pint in 4 hours, also a large transfusion must be avoided, otherwise heart failure may readily ensue. Normally, a healthy subject who has lost much blood may be transfused as rapidly as a pint in three minutes for the heart is normal, and, in fact, very rapid transfusion may be necessary to save life.

Transfusion may be effected by any of the following techniques.

1. *Venepuncture.*—The transfusion apparatus connected with the bottle is suspended 3 or 4 feet above the patient and tested. The "giving needle" as yet unconnected, is inserted under local anæsthesia into a vein and, immediately reflux of blood occurs, is connected with the transfusion set. This will ensure that the transfusion fluid is injected into the vein and not into the tissues around it. Arm and leg veins are commonly used, though sometimes it may be necessary to use other veins such as those of the scalp or neck. A forearm vein should be selected in preference to one in the antecubital fossa. Limb veins may be rendered prominent by constricting the limb proximal to the vein with a sphygmomanometer cuff by manual pressure. Practically all transfusions can and should be given by simple *venepuncture*.

Cannulation of veins.—Cutting down on a vein and tying in a cannula is seldom justifiable. Scarring may result and the vein is likely to be rendered useless for further transfusions.

Intramedullary transfusion.—Blood injected into the bone marrow is soon absorbed into the circulation. Owing to the risk of osteomyelitis, intramedullary transfusion should be used only when a vein is not accessible for *venepuncture* or cannulation. In adults the sternum or clavicle may be used. In infants the upper end of the tibia is suitable, but not the sternum.

Complication of technique.—Hæmatoma, sepsis or thrombosis are due to faulty techniques. Fatal air embolism may result from leakage of air into transfusion apparatus through faulty connexions.

Transfusion reactions.—Fever, rise in pulse rate, chills, rigors, pains in head, chest and back, circulatory failure may all occur. Pyrogens in solutions or residual blood substances from inefficiently cleaned tubing may cause sharp pyrexial reactions. Allergic reactions, such as urticaria, or sometimes angioneurotic oedema, may complicate about 1 per cent. of transfusions. Treatment should be with adrenaline and calcium gluconate. Homologous serum jaundice is a late, and usually serious, complication of

transfusion, but the incubation period is usually a long one, being between 40–150 days. Then symptoms of hepatitis, anorexia, malaise, headache and vomiting, with perhaps skin rashes and urticaria, supervene, followed in a few days by jaundice. The mortality may be high and about 5 per cent. The incidence after blood transfusion is about 0·8 per cent. It is known that this disease can be transmitted merely by the injection of a single drop of plasma, serum or blood. It was at one time prevalent in some hospitals, venereal wards and diabetic clinics, and was due to insufficient sterilization of syringes and needles. More efficient methods of sterilization have abolished it. It appears that about 0·4 per cent. of the population harbour the causal virus in their blood.

Concentrated human red blood corpuscles.—(Packed Red Cells). This is concentrated human red blood corpuscles in whole human blood from which not less than 40 per cent. v/v of plasma and anticoagulant has been removed. It is a dark red fluid, but after standing, the red blood corpuscles may form a sediment, leaving a supernatant layer of yellow plasma. Concentrated red blood corpuscles are prepared from stored blood aged up to 7 days, the supernatant plasma being filtered off under strictly aseptic conditions. An alternate method is to use fresh citrated blood packed down by centrifugation and the supernatant plasma then drawn off. It is, of course, essential that the whole blood should have been matched with that of the recipient. Commonly, the red blood corpuscles from two bottles of blood are concentrated into one. The bottles should be stored in sealed containers at a temperature of 4°–6° C.

The transfusion of concentrated red cells has special application to anæmias not due to hæmorrhage and also to anæmic states due to persistent bleeding.

A simpler method of giving packed cells, which has been used many times, is to insert the giving set of tubing, etc., and to suspend the inverted bottle for 30–60 minutes before inserting the needle into the recipient's vein and starting the flow. This allows the red cells to sediment; the transfusion is stopped and the bottle changed to another similarly prepared, as soon as all the red cells have been exhausted, leaving only the supernatant plasma in the bottle. This method obviates opening and manipulating the bottle before transfusion, always a dangerous procedure.

CHAPTER LII

DDT AND OTHER INSECTICIDES

THE application of DDT opened up an epoch, which, probably more than any other measure, led to the conquest of insect-borne disease, malaria in particular. The result has been that some 50 insecticides are now listed for Pest Control.

It is not possible to deal with all of them in this work, so that only the most important in the realm of Tropical Medicine will be considered.

DDT. *Chlorophenothane*, *Dicophane*—a white amorphous powder—is prepared from chloral and chlorobenzene. It is not normally decomposed by sunlight. DDT may be effectually included in paints and washes for the treatment of walls to make them residually insecticidal. The method is successful with casein-paints, calcinines and chalk whitewashes. A concentration of 3-5 per cent. in flat-oil paints is very effective.

DDD is an analogue of DDT which has one chlorine atom less. It is produced by condensation of dichloroacetal with chlorobenzene and is marketed as a 50 per cent. wettable powder (e.g. Rhothane, W.P. 50).

B.H.C.—Benzene hexachloride—contains 44.8 per cent. of chlorine and consists of crystals with a musty odour. It is prepared by the chlorination of benzene in the presence of ultraviolet light. Benzene hexachloride consists of a mixture of optical isomers of which the *gamma* isomer is the most important and is known as *gammexane*, though it should be more correctly known as *lindane*.

Chlordane (chlordan) is a highly viscous liquid with a turpentine-like odour. It occurs as *alpha* and *beta* chlordane. Further derivatives are *hexachlor* and *heptachlor*. Of these the latter is 4-5 times as insecticidal as chlordane. Emulsion concentrates containing 45-75 per cent. Chlordanes are made by mixing the product with *kerosene* and adding 10 per cent. of a wettable agent.

Wettable powders are made by spraying chlordane, treated to 130° F., on to diatomaceous earth to give a 10 per cent. mixture.

Aldrin is a white crystalline solid with a melting point at 100-108° C., but when warmed it has a pine-like odour. It is much less volatile than *lindane* and in residual effectiveness it is half way between it and DDT. Insoluble in water, it is soluble to 89 per cent. in kerosene at 26-30° C.

Diieldrin is a derivative of aldrin. This is an odourless, white crystalline solid, with a melting point at 178° C. It is scarcely volatile, but showing a residual toxicity, with a persistence comparable to that of DDT. It is the most toxic and residually most effective of the insecticides.

Toxaphene is a chlorinated camphene, containing 67-69 per cent. of chlorine. It is a cream-coloured waxy solid with a mild terpene odour and is insoluble in water and scarcely volatile, though highly soluble in organic solvents and oils. Thus, kerosene will take up more than 280 gm. per 100 ml. at 27° C. Oil solutions can be stored in clean glass bottles without deterioration.

The organic phosphates have not so far come into wide use for malaria control owing to their toxicity.

HETP, *hexaethyltetraphosphate*, is a mixture of linear polyphosphates. The main insecticidal principle is *tetraethylpyrophosphate* or TEPP. (malathion). HETP is a light amber, oily liquid with a freezing point at -40°C . It was originally produced in Germany as a 60 per cent. emulsion under the name of *Bladan*. Both TEPP and HETP are readily miscible with water to the extent that they are hygroscopic. They are miscible with organic solvents and aromatic oils, but not with kerosene or other paraffin oils.

Parathion is a principal insecticide, slightly soluble in water, but miscible with a variety of alcohols, ethers and esters and soluble in certain vegetable oils, but virtually insoluble in kerosene. It is relatively non-toxic and effectual for houseflies resistant to DDT.

These phosphorus compounds—parathion in particular—must be used with great caution and require gas masks and protective clothing for operators. They are extremely poisonous, orally, cutaneously or by inhalation.

EPN, *ethyl-p-nitrophenyl thiobenzene phosphonate*, is an effective acaricide and a promising insecticide. It is slightly soluble in water and is produced as a 27 per cent. wettable powder.

The organic thiocyanates. These insecticides have been developed for their knockdown properties in fly sprays; most of them are known as *Lethanes*. Lethane is a mixture of 12.5 per cent. β -butoxy- β -thiocyanodiethyl ether with 87.5 per cent. β -thiocyano-ethyl laurate in 50 per cent. petroleum distillate.

Organic compounds of vegetable origin.—The pyrethrin compounds, as found in pyrethrum flowers, consist of 4 esters known as *Pyrethrins I and II* and *Cinerins I and II*.

The pyrethrins and cinerins are extracted from the dried flower heads of *Chrysanthemum cinerariæfolium* which is now cultivated in Kenya and Japan. The active principles can be extracted with alcohol or acetone and, after evaporation of the solvents, appear as an oleoresin. Stored pyrethrum powders lose 20 per cent. of their insecticidal activity in one year.

The pyrethrins may be extracted in kerosene and sold as concentrates (*Pyrefume super 80*). They may be further diluted in odourless kerosene to 1 per cent. content and used as household fly sprays.

Pyrethrin synergists.—Certain compounds have the effect of enhancing the toxicity of pyrethrins so that much less pyrethrum is needed in the spray with synergist to achieve the knockdown of flies. An example is piperine, a crystalline solid obtained from black pepper.

Mode of action of insecticides on insects.—The outstanding factor in the effectiveness of DDT as an insecticide is that, for a great number of insects, the lethal dose required by contact application is almost as low as the dose by injection—namely about 10 mgm./kgm. The cuticle of these insects does not constitute a protective barrier to the entry of this poison. Suggestions have been made that the DDT-poisoned insect dies from exhaustion resulting from muscular tetany during the final

stages of paralysis and from intoxication of metabolites which accumulate in the muscles during their continued state of contraction.

Methods of application with special reference to DDT and BHC.—The essential requirements for the application of insecticides in the field is the formation of small crystals or particles, 10–20 μ in diameter, which can be easily picked up by insects, mosquitoes especially. For the preparation of wettable powders, or suspensions, it is necessary to grind the dust as finely as is, for instance, necessary for the manufacture of paints. Persistence is the most valuable property so that surfaces contaminated with it will poison insects that rest upon them for many weeks.

To apply a good deposit, kerosene solutions containing 5 per cent. and 0.5 per cent. respectively of these two insecticides are adequate. Gamma BHC is much more toxic than DDT so that mosquitoes die with a lethal dose after a very brief contact period. An oil with a high spreading pressure is necessary in order to form a powerfully spreading film over large areas despite the presence of aquatic weeds. A suitable oil (containing resin) should be sprayed with a dosage of about 2 ml. per 100 sq. feet.

DDT and BHC can be incorporated in paint or distemper, but then power is less than when applied directly. The crude insecticide is broken up on a tile or on a concrete floor and, when pressure is applied, a soft sticky mass is produced which is then made into a smooth paste.

Aërosol mists, such as the aërosol bomb, in which DDT is mixed with a liquid gas (*dichlor-difluor-methane* = Freon) in a closed container. In the Freon bomb carbon dioxide is used in small insecticidal sprayers. On opening a fine nozzle the liquid is driven out and forms a fine mist which has a transient insecticidal effect. The composition is: DDT or BHC 3 per cent., lubricating oil 5 per cent., pyrethrin 0.3 per cent. dissolved in Freon. These aërosols, when released 1–2 ft. from the ground level, can be used to put up a barrier around any chosen area. Insecticidal smokes are clouds of insecticidal particles produced without the agency of a carrier fluid and are similar to aërosols.

Sprayers are of many types. The 4 gallon compression, or *pneumatic sprayer*, consists of a cylinder approximately 20 ins. in height and 7½ ins. in diameter. When equipped with 3 ft. of hose terminating in a trigger, rod and nozzle, it can be slung over the shoulder. The *Knapsack sprayer* is constructed to fit the back of the operator. The pump is activated by a lever carried forward to the operator's hand for up and down arc movement and it is provided with a small air chamber for pressure stabilization.

Application of insecticides from aircraft.—Under modern conditions aeroplanes are much used for the widespread application of insecticides. The Stearman is most suitable. The ideal is a low-wing monoplane, of all metal construction with bolted wing-sections powered by not less than 200 h.p. to carry 1,250 lb. pay load at 60–70 miles per hour. Solutions are used at 5 per cent. at the rate of 2–4 quarts per acre. The greater the concentration of the spray-fluid the greater the area that can be covered by aircraft. This method has given good results in India, Burma, and in U.S.A., but in some countries, such as Italy, where the

adult insects commonly rest in houses and stables, the results have not been so good. The fine liquid spray is effected through an emission tube, or *venturi*, under the fuselage, or through a boom with nozzles on the underside of the wings. Smokes and aerosols can be produced by a plane by injecting solutions of insecticides into exhaust stacks and relying upon the heat and exhaust to break them up into very fine particles. The best results are obtained at heights from 25–80 feet. Helicopters are employed to kill anophelines of the genus *Kerteszia* which breed in the axils of bromeliads. The effects obtained are mainly due to the extermination of adult mosquitoes.

Insecticidal action on mosquitoes.—The control of mosquito larvæ has been revolutionized by the appearance of DDT and it is as toxic to them as to the pyrethrins, giving a complete kill at 0.01–ppm. in water and it is, in fact, 100 times as toxic as Paris Green showing an LD₅₀ of 0.0025 ppm. against *Anopheles quadrimaculatus* and complete control of mosquito larvæ can be obtained with 0.005 lb./acre in shallow water under laboratory conditions. Under field conditions the doses of 0.5 lb. per acre has been found to be comparatively inefficient. Therefore DDT is usually applied as a 5 per cent. solution in kerosene or fuel oils, giving almost complete control of mosquito larvæ under the conditions of aircraft spraying. The best solvents are kerosene or diesel oil No. 2. In the case of stream breeders (*A. minimus flavirostris*) in the Philippines, contact with larvæ is best effected by sawdust impregnated with 2 per cent. DDT solution. This practical larvicide is made of two parts of sawdust and one part of plaster of Paris by volume, mixed with water and allowed to set. The mixture is cut into pellets of 0.5–1 cm. and dried for 48 hours. They are then soaked in DDT in oil for a similar period. These pellets can be thrown for a considerable distance to breeding places which are difficult of access, and this method is especially adapted for rice fields.

Malariol (a special paraffin solution, see p. 88) with 5 per cent. DDT solution, half a gallon per acre, gives the best control against anopheline larvæ and its spreading power is greatly assisted by the addition of 0.25 per cent. resin, or 0.5 per cent. Trilon B, 1956 (*alkylated aryl polyether alcohol*).

Aerosols are quite satisfactory as larvicides. *Parathion* (E-605-O, 3-diethyl-o-p-nitrophenyl thiophosphate) is the only other insecticide that rivals DDT in its toxicity to mosquito larvæ and is available as 15 per cent. wettable powder.

Dieldrin—25 per cent. wettable powder and a dust containing 25 per cent. of active material (of which a stock suspension is prepared by mixing 0.12 lb. of powder in 1 gallon of water) and applied at the rate of 5 quarts per acre. *Dieldrin* H.S.D. is a high-spreading antimalarial oil, similar to malariol, but containing dieldrin, is sprayed on the surface at the rate of 0.5–1 gallon per acre. It is claimed that better results are obtained than with DDT or BHC. The toxic effect of DDT gradually disappears in time because of its absorption into the vegetation.

Action on adult mosquitoes.—Generally-speaking anophelines are more susceptible to insecticides than are culicines.

DDT is used in sprays in combination with pyrethrum to ensure a quick "knock down." Such a spray is 0.05 per cent. pyrethrin, with 5 per cent. sesame oil and 0.3 per cent. DDT in kerosene and given at the rate of 1 fl. oz. to every 3,000 cu. ft.

Sesame oil augments the insecticidal properties of pyrethrums and also piperine derivatives, especially piperonyl butoxide. There is also a synthetic product "Allethrin" which has many properties in common with pyrethrum.

Pocket-size sprays can disperse insecticides with the following formula: 30 per cent. DDT, 20 per cent. cyclo-hexone, 5 per cent. motor oil, and 0.2 per cent. pyrethrum in kerosene. Spraying of the internal surfaces of houses is the commonest method. Most anophelines enter houses to feed for 5-6 hours, and after completion of their meal, rest on the walls and ceiling. Some, such as *A. darlingi* in British Guiana, remain for two or three days; others, such as *A. albimanus* and *Kerteszia aquasalis* for only a few hours, and others like *A. maculatus*, in Indonesia, Ceylon and Malaya, not at all. Treatment of huts in British Guiana with 100 mgm./ft. gave a resident population reduction of 99 per cent. of *A. darlingi*. Spraying of houses, once every 9-10 months, has practically eliminated malaria. For the residual treatment of walls, DDT is superior to other chlorinated hydrocarbons on the basis of the power of initial kill and the duration of its toxicity. In this respect DDT is better than BHC, chlordane or toxaphene.

At a deposit of 200 mgm./sq. ft. DDT continues to kill mosquitoes for a period of 15-36 weeks as against 4 weeks with BHC or chlordane. On clay walls, which absorb DDT, BHC may be superior. On absorbent surfaces, such as dried mud, serious losses of DDT and BHC solutions occur.

Most health authorities now use *wettable* powder suspensions for large-scale operations. When applied by knapsack pressure sprayer, at doses of 100-300 mgm./sq. ft., results are more permanent.

BHC possesses an initial toxicity especially to African anophelines (*A. gambiae*, *A. funestus*, *A. moucheti*), in the form of *wettable* powder when applied at six monthly intervals at the dose of 13-15 mgm. *gamma* isomers per sq. foot, and in Tanganyika experiments with BHC dispersible powder show that the lethal action against *A. gambiae* persists for 3 months.

Residual outdoor spraying is of value for mosquito destruction and leads to reduction of larvæ as well. BHC, when applied to walls of houses, barns and tents (50-100 mgm. per sq. foot) remains active for 2 months.

Dieldrin is recommended as a new insecticide for mosquitoes by many authorities for its outstanding effectiveness at low economic dose. When sprayed on all surfaces, an adequate residual action is obtained by application of 10 mgm. per sq. foot.

Action on simuliidæ.—DDT is an extremely potent insecticide for the larvæ of simulium. Very small concentrations in water cause them to detach themselves from stones, to wash down the stream and then to be killed in DDT-treated water. It has been found that a concentration of 0.1 ppm. of DDT suffices to clear streams in Guatemala for 1,000 yards downstream.

Treatment of rivers at doses, averaging 2-10 ppm. of DDT, completely eliminated larvæ of *S. neavei* over an area of 65 square miles in Kenya.

The discovery that there exists a phoretic association of the pupæ and larvæ of *S. neavei* with river crabs in Kenya has a bearing on the application of DDT to rivers for the important vector of onchocerciasis. It is now necessary to treat only those rivers which are inhabited by this crab (*Potamon niloticus*). The principle of this DDT treatment is to apply an oil emulsion to the running water to maintain a concentration of at least 2 parts DDT per million parts of water for 30 minutes, repeating the process once every 10 days in order to kill successive batches of larvæ and checking the results for adult flies. The most successful mixture was 20 per cent. DDT in toluene, with 10 per cent. soap and 1 per cent. "Abracol" as a stabilizer. The emulsion is applied from drip cans suspended over the water. Larvæ and pupæ rapidly disappear and adult simuliidæ can no longer be caught one month after the start.

There is no evidence of differences in susceptibility between different species of *Simulium*. Methoxychlor and DDT are equitoxic with DDT and are superior to chlordane, toxaphene, BHC, and even lindane.

Action on midges (Culicoides).—These insects are very difficult to control in the larval stages since they breed in damp organic matter in swamps. With *C. furens* in Panama it was found that area sprays were useless to reduce the adult population of culicoides.

Action on psychodidæ.—Sandflies. DDT has proved to be most efficient in the control of sandflies. Spraying houses, walls and caves with 5 per cent. DDT in kerosene has given long-lasting control of species of *Phlebotomus* in Peru.

Application of DDT at 100 mgm. per sq. foot has also given protection against *P. papatacvi* and other species in controlling sandfly fever in Greece and the Levant.

On the whole, the adult insects are highly susceptible, and the larvæ are more resistant. Complete protection can usually be obtained by DDT and BHC residual sprays when special attention is paid to corners and upper parts of the walls, doors, windows and screens. Outside spraying of walls, especially in Turkey, where cow dung is commonly used and rubble heaps are the mode, destroys sandflies before they have a chance of entering buildings. In Greece the standard method is by hand pressure sprays of watery emulsions of DDT.

Action on bed-bugs.—Of all the insect pests the bed-bug (*Cimex lectularius*) is most susceptible to the action of insecticides. It has been found that DDT sprays and even dusts, when applied to the crevices of buildings as well as to bedding, gives excellent control of bugs. Suspensions and solutions of 5 per cent. DDT show a residual toxicity for as long as 200 days, while 20 per cent. sprays give a highly effective protection for dwellings for 11 months. The application of DDT to houses in the metropolitan centres in New York is fast eliminating the bed-bug.

The next most powerful agent is *methoxychlor* which is almost equally as effective as DDT and superior to other analogues.

Toxaphene is less toxic than DDT as a residual deposit, and even more so than by direct contact, but with *lindane* and *p-chlorophenyl chloromethyl sulphone* are more toxic than DDT to the bed-bug.

Action on reduviid bugs.—Gamma BHC is, generally-speaking, more effective than DDT. Dias and Pellegrino have used a watery emulsion in 1–2 grm per sq. m.

Adults are more susceptible than nymphs, but when they infest mud walls the toxicity is more effective. Smokes and aerosols are usually employed for this purpose in Argentina. Spraying with BHC (see p. 854) in 7.5 per cent. suspensions in water is used against *Triatoma infestans* in Uruguay. The results are satisfactory, even after a nine months' interval. DDT dusts are lethal to both *Triatoma* and *Rhodnius* in Brazilian huts.

It has been shown that the blood of living pigeons can be rendered lethal to *R. prolixus* by the oral administration of DDT in doses of 200 mgm. per kg.

Action on fleas.—Dwellings may now be freed of the human flea (*Pulex irritans*) by 5 per cent. DDT dusts or sprays. The oriental rat-flea (*Xenopsylla cheopis*) may be countered by dusting rat runways with 8 per cent. DDT and this treatment, along with DDT-impregnated clothing, was successful in protecting allied armies during an outbreak of bubonic plague in Casablanca in 1945.

The dog-flea (*Ctenocephaloides canis*) may also be eliminated by dusting dogs with 5 per cent. DDT, in addition to cleaning houses and kennels with 10 per cent. DDT dust applied at 0.5 lb./1,000 sq. feet, or by DDT spray applied at 1 gal./1,600 sq. feet.

Action on lice.—DDT has completely revolutionized delousing policy. *Anti-louse powder* contains 10 per cent. DDT. The chief advantage is that the individual can be treated fully clothed.

Three treatments at weekly intervals suffice for elimination of nits and lice. For mass treatment special dusting teams are organized. For head lice powder is applied direct to the head and nape of neck.

Impregnated clothing.—Angola drab shirts are impregnated at the rate of 1 per cent. DDT weight for weight of garment. The shirts are referred to as A/T (*Anti-typhus*) and have proved most effective. If unwashed such a shirt affords complete protection for eight weeks and considerable protection for yet another four. Washing by a special process of the mobile laundry destroys the efficacy of DDT after the third washing.

For impregnation of garments the powder is insufflated by a blower into the loosened clothes. Of the various kinds the Dobbin (Superbilt) Duster or the Hudson (Admiral) are the best, though one of the horticultural types may be employed with the nozzle shortened to project about 8 in. beyond the barrel. The aim should be to insufflate powder in pyrophyllite and mixed with air with an average of 1½–2 oz. for each person. The head covering should be treated, and then, with arms extended, the delivery tube should be inserted into both sleeves and powder pumped between the skin and singlet, paying special attention to armpits and shoulders.

Inserting the tube in front, the chest should be sprayed from one side to the other. Next the tube should be inserted into the neck-band and the back should be dusted. The legs are treated through the trousers, especially the crutch and pubic areas. The waist, side seams and rear of pants are powdered in turn, especially over the buttocks and rear of the crutch. When no blower is available the powder can be well shaken into clothing removed from the body. With the coat laid open on the table the whole inside and armholes are dusted. The trousers are treated in the same manner. By these means a team of two can treat 30–40 persons in an hour. The powder remains active for two to three weeks.

DDT is not ovicidal and has maintained its position as the best lousicide in spite of examination of literally thousands of other compounds.

DDT powder is effective also against the head louse (*Pediculus h. capitis*). For this, liquid formulæ are preferred since they are not noticeable in the hair; oils containing pyrethrin are also highly effective and do not irritate the skin.

The latest formula consists of 1 per cent. DDT emulsified in 11 per cent. benzyl benzoate as the solvent, with *Tween* 80 as the emulsifier. To this 2 per cent. benzocaine is added to eliminate irritation and to act as an ovicide. This is known as NBIN.

The crab louse (*Phthirus pubis*) is controlled by an emulsion containing lauryl thiocyanate and by salves containing *Lethane* 384. (*Lethane* 384 is a mixture of 12·5 per cent. β -butoxy- β -thiocyano-diethyl ether with 37·5 per cent. β -thiocyanoethyl laurate in 50 per cent. petroleum.)

Insecticidal action on mites.—Experiments in Malaya show that dieldrin, aldrin, chlordane, toxaphene and lindane are promising in control of *Trombicula akamushi* and *T. deliensis*, the vectors of scrub typhus.

Dieldrin and aldrin were tested against these mites in the field. After estimating the mite population in three areas by trapping *Rattus rattus* and *R. mülleri* and releasing them in fenced plots, they were sprayed by insecticides. Dieldrin was used as 1·5 lbs. to the gallon, aldrin 2 lbs. to the gallon and showed a marked reduction of mites within 3 days.

Insecticidal action on ticks.—The soft tick—*Ornithodornus moubata*—is comparatively resistant to DDT but is susceptible to BHC.

The best results have been obtained with a water-dispersible powder, P 530 (containing 6 per cent. gammexane). The action is high against ticks of sheep and cattle and also against *Argas* and *Boophilus*.

In East Africa a preparation known as D220, or agroicide 7, contains 2·5 per cent. gamma BHC one part, mixed with 4 parts of diatomite to produce a light powder, called G dust, applied at the rate of 3 lb. per 1,000 sq. feet.

Regular treatment of houses has achieved comparative freedom from *O. moubata* and almost complete disappearance of tick-borne relapsing fever.

Insecticidal action on tsetse flies.—Tsetse flies (*Glossina* of all species) are very susceptible to DDT by direct contact or by residual contact with their pulvilli. A certain measure of control can be obtained by hanging cloth screens, treated with DDT, to act as traps at strategic

points throughout the bush and jungle. On the other hand the vegetation may be sprayed at points where the flies congregate. About 98 per cent. control may be obtained by spraying 4 times at weekly intervals with DDT at 100 mgm. per sq. foot, or lindane at 11 mgm. per sq. foot. When fly areas are treated with DDT, applied by a thermal aerosol generator, about 50 per cent. control is obtained. BHC smoke with a range of 60 yards in bush gives up to 90 per cent. control. The spraying of cattle with 9 per cent. DDT solutions, three times weekly, has been found to kill 90 per cent. of female *Glossina pallidipes* feeding on them, to achieve 80 per cent. reduction in the infestation level on the area. Recently it has been found possible to treat calves orally with BHC at 250 mgm./kg. weekly and so to render them toxic to glossina.

DDT spread by aeroplanes has been carried out in Zululand (du Toit and Kluge, 1947). The area was sprayed three times over a period of five weeks. This procedure was adopted on the assumption that the first two applications would cover the normal gestation period of the flies. A 20 per cent. solution of DDT was dissolved in four parts of toluene oil and seven parts of C.I. fuel oil. This was fed at the rate of 5 gallons per engine per minute representing an output of 16 lb. DDT per minute. It was estimated that DDT would penetrate the dense foliage and be deposited on the undersurface of the leaves.

Action on houseflies.—DDT acts only on adult flies. It is used as a direct spray, or as a residual spray in breeding areas. In the direct spray the addition of 0.3 per cent. pyrethrum gives the necessary "knock down." DDT dust is most effective in 1–2 gm. per sq. foot. On manure heaps DDT acts only if not covered up. *Musca domestica*, the housefly, possesses the amazing power of resistance to insecticides which it has rapidly developed. Already in 1946, two years after the introduction of DDT into Italy, resistant houseflies were noted near Rome, Naples and other parts of the country, while at Arnas in Northern Sweden resistant flies were found where DDT had never been used before. Resistance to organo-phosphorus compounds has been reported from Italy and Switzerland.

Toxic effects of DDT.—Some preparations of DDT under certain conditions do involve some risk to man. Certain oily preparations and DDT distemper may be toxic and fatal cases have been reported from drinking 5 per cent. solution in kerosene, the symptoms of which resemble those of carbon tetrachloride poisoning.

Prevention of noxious insects in aeroplanes.—Regulations for quarantine disinfection were developed in 1930. They require the use of an aerosol containing no less than 1 per cent. pyrethrins and 8 per cent. DDT at the rate of at least 5 gm. per 1,000 cu. feet. The typical formula is:

Pyrethrum extract (20 per cent. pyrethrum)	5
DDT (percentage by weight)	8
Cyclohexanone	5
Lubricating oil	2
"Freon 12"	

Disinfestation may be carried out whilst in flight, but must be accomplished at least half an hour before arrival. The ventilation system must be closed whilst the insecticide is released and for three minutes afterwards.

Insecticide resistance.—True resistance to insecticides has developed in *Anopheles maculipennis*, *A. superpictus*, *Phlebotomus papatasi* in Greece, *Triatoma infestans* in Chile, *Anopheles philippinensis* in India, *Stomoxys calcitrans* in Spain and in various species of fleas.

The subtropical and tropical varieties of the housefly are now, nearly everywhere, more or less resistant to all newer chlorinated insecticides. More recently signs of resistance have appeared in the field where organo-phosphorus compounds have been used for practical control. It may well be that it is a little too early to abandon hope of using organo-phosphorus as insecticides for fly control, but there is no future as for the chlorinated compounds.

On the other hand mosquitoes were some of the first insects to be systematically attacked by residual insecticides and many species have been under control with DDT for more than 10 years of spraying. In spite of this, the susceptibility of *Anopheles atroparvus* in Spain, Sardinia and Italy, *A. culicifacies* in Ceylon and India, of *A. pseudopunctipennis* in Mexico, or of *A. darlingi* in British Guiana, remains.

In the case of *A. sacharovi* in Greece, resistance suddenly appeared in 1951 and has now become widespread. In recent years chlordane and dieldrin have been used instead and *A. sacharovi* has become resistant to them also. Resistant strains of *A. sudaicus* were discovered near Tjarkarta and a high resistance at Soemerang, but strangely no resistance has as yet developed in other local anophelines, such as *A. subpictus* or *A. aconitus*. These insects were, however, moderately resistant to gamma BHC, but not significantly resistant to DDT. This quality of resistance is transmitted on a Mendelian basis. In Southern U.S.A. proof has been obtained of high resistance to dieldrin, chlordane and gamma BHC, but retaining normal susceptibility to DDT.

The example of *Anopheles stephensi* in Saudi Arabia as the result of DDT house spraying in 1947 has been revealed. Resistance to DDT was rapidly developed, but this mosquito is found to be susceptible to dieldrin. Various species of culicines showed signs of insecticidal resistance in U.S.A. when sprayed from the air.

As regards *Aedes aegypti*, this species was eradicated during anti-anophe-line campaigns in Greece, Mauritius and in British Guiana, but in Trinidad a different story was revealed. Commencing in 1951, 80,000 houses were sprayed in Port of Spain and suburbs, without effect upon the numbers of *A. aegypti*. Where this mosquito comes into contact with DDT used for malaria it became resistant in Haiti and Venezuela.

Following the failure of DDT antilarval treatments in the field, laboratory-bred colonies have been found to have a high resistance to DDT. So far, however, there has been no resistance to dieldrin or gamma BHC. *Culex fatigans* is a mosquito with a high natural resistance to insecticides, so that treatments which produced a high proportion of kills in local anophelines, caused only a low mortality in this species, but no evidence of enhanced resistance was found later.

Resistance in lice.—Resistance has now revealed itself in the body louse *Pediculus h. humanus*, but there is no evidence so far of resistance in the head louse (*P. h. capitis*) or in the crab louse *Phthirus pubis*.

The first failures to control typhus and lice occurred in the P.O.W. camps in Korea and some time after practical application proved the existence of high-level resistance. Similar observations were made in Japan and a strain of lice collected in Cairo were found resistant.

The final position is as follows: While DDT still remains satisfactory in controlling lice in most places, it is possible that failures may occur in areas outside Europe, so that it cannot be guaranteed as a universal anti-lice measure. So far *gamma* BHC dust could be a reliable substitute everywhere and although there are now ominous suggestions of commencing resistance, Pyrethrum powders remain as the final rampart in insecticidal defence against louse-borne epidemics.

Bed-bugs.—House-spraying with DDT initially enormously simplified the task of destroying bed-bugs in old houses. Now reports of resistance have come in from many countries, including Greece, Italy, Israel, U.S.A., the Belgian Congo and China. *Cimex hemipterus* appears to have become resistant in Hong Kong, Formosa and Singapore. This species is much more resistant to DDT than normal *C. lectularius*, though slightly more susceptible to *gamma* BHC. Up to the present resistant bugs in Hong Kong and Singapore appear to be normally susceptible to *gamma* BHC and dieldrin. These bugs in Israel and parts of Tanganyika have become resistant to dieldrin, BHC and others of the group.

Fleas.—From 1944 to 1948 DDT dusts used against fleas (*X. cheopis*), substantially reduced murine typhus in parts of the U.S.A. and checked outbreaks in Dakar (Senegal), Haifa, Ngamiland (S. Africa), Peru and Ecuador.

In several instances large populations of the cat flea (*Ctenocephalides felis*) have persisted, even after three applications of 5 per cent. DDT pyrophyllate dusts to infected premises. With the use of 5 per cent. chlordane dusts the number of infestations dropped markedly.

Two general kinds of resistance have recently become prominent:

- (1) to DDT and analogues.
- (2) to *gamma* BHC and compounds of the chlordane type and to organophosphorus insecticides.

After the housefly had become resistant to DDT, other chlorinated insecticides were used, but it was soon found that when a new resistance developed, either to chlordane or to *gamma* BHC, the flies automatically acquired resistance to several other insecticides.

Overcoming existing resistance.—The present position appears to be as follows: Instead of changing to another insecticide a possibility is to change to other measures which may be feasible, if resistance develops in the later stages of a campaign. Thus, when the use of insecticides for several years has drastically reduced a disease, such as malaria, it may be possible to eliminate the residue by distribution of drugs that might not

have been originally feasible. Another method with possibilities has recently been developed. Thus when the insect population has been greatly reduced by insecticides, males, sterilized by radio-activity, are released which, in turn, prevents the female with which they mate, from breeding. This method has been successful in eradicating the screw-worm (*Callitroga*) from the island of Curaçoa.

CHAPTER LIII

TABLE OF DRUGS FOR TREATMENT OF TROPICAL DISEASES

COMPOSITION, INDICATIONS AND DOSAGES

This list has been drawn up in alphabetical order to afford ready assistance to the student and practitioner. In most cases the common or pharmaceutical name of the drug is given, with synonyms (in italics), chemical constitution, therapeutic application, dosage, spacing and other relevant information.

The Editor is indebted to Mr. R. Ferrier, M.P.S. of May and Baker, for considerable assistance in this section.

Acidum Ascorbicum B.P. *Vitamin C, Cevitamic Acid, Proscorbin, Redoxon.*

Enolic form of 3-keto-1-gulofuranolactone.

Scurvy, Wound healing.

Oral, tab. *acidi ascorbici* 50 mgm. three times daily. Intravenous, in acute cases.

Acranil.

Hydrochloride of an acridine derivative.

Giardiasis, Balantidiasis.

Oral, tablets of 0.5 grm. Three tablets daily (1.5 grm.) for five days. Used in Germany and Scandinavia. No toxic effects. (*See p. 501.*)

Alicopar. (B.W.)

Bephenium hydroxynaphthoate (benzyl-dimethyl-2-phenoxyethyl-ammonium).

Ancylostomiasis, ascariasis.

Oral, 2-3 grm. for adults; children, single daily doses of 2 grm. for 4 days.

No purgation necessary.

Amphotericin.

Antibiotic.

Cryptococcosis and Coccidioidomycosis, Mycetoma.

Oral, 3 grm.-12 grm. daily to total of 215 grm.

Intravenous, 1 mgm. per kgm. Total dosage 1 grm. over a period of 18 days.

Aneurin. *Aneurinæ Hydrochloricum B.P., Thiamine Hydrochloride, Vitamin B₁.*

3-(4'-Amino-2'-methylpyrimidine-5'-methyl) 5-B-hydroxyethyl-thiazolium chloride hydrochloride.

Beriberi, Burns, Varicose Ulcers.

Oral, tablets 3 mgm. Injection, 25 mgm. in 1 ml. Store protected from light.

Anthical.

Zinc oxide and anthisan.

Lotion for sunburn and insect stings.

Anthiomaline.

Lithium antimony thiomalate.

Schistosomiasis, Lymphogranuloma inguinale, Leishmaniasis, Filariasis (*W. bancrofti*).

Intramuscular or intravenous, 0.03-0.12 grm. ($\frac{1}{2}$ -2 gr.).

6% solution: 4 ml. for adult, 2 ml. for children.

On alternate days for 10 or more injections.

Anthiphen (M. & B.). *Dichlorophen.*

2 : 2'-dihydroxy-5 : 5'-dichloro-diphenyl methane.

Tæniasis. *Tænia saginata.*

Oral. Tab. 0.5 grm. for adults, on two successive days. For mass treatment 6-9 grm, single dose.

Anthisan. *Mepyramine maleate B.P.*

A potent antihistaminic for the treatment of allergic conditions as in filariasis and schistosomiasis.

Oral, 0.3 grm. increasing to 1.0 grm. daily, in divided doses, taken only with food.

Antimonii et Potassi Tartras B.P. *Tartar Emetic.*

Kala-azar, Oriental sore, Espundia, Lymphogranuloma inguinale, Ulcerating granuloma, Trypanosomiasis, Relapsing Fevers, Leprosy reactions, Schistosomiasis.
Intravenous, in solution in distilled water, 0.03–0.12 grm. (0.46–1.8 gr.).
Alternate days—up to total of 2.5 grm. (38.5 gr.).

Antimony dimercapto succinate. (*T.W.Sb.*) (Friedheim).

Soluble in water—30 %.
Schistosomiasis (*S. haematobium* in Rhodesia; *S. mansoni* in Brazil, but less effective in Rhodesia and S. Africa.
Intramuscular injection 0.5 grm. Total 32 grm. (49.2 gr.).
13 days: 23–42 mgm. per kg.
Intravenous 0.7–2.3 grm. total (10.8–35 gr.) for 3–5 days. (*See p. 701.*)

Antimosan. *Von Heyden* 661.

Potassium antimonyl pyrocatechol-sulphonate. Contains 12.5 per cent. antimony in trivalent form.

Kala-azar and other forms of Leishmaniasis.
Intravenous or intramuscular, 0.2 grm. (3 gr.).

Antrenyl (Ciba).

2-diethylaminoethyl- α -cyclohexyl- α -phenylglycollate methobromide.

Antispasmodic for relief of gastro-intestinal pains.
Oral. Tab. 5–10 mgm. (0.07–0.15 gr.), four times daily.

Antrycide chloride. (Curd & Davey, 1949.)

4-amino-6-(2'-amino-6'-methylpyrimidyl-4'-amino)-quinaldine-1 : 1'-dimethochloride.

Trypanosomiasis of cattle and man.

Injection : single dose of 1 mgm. per kg. for *Trypanosoma congolense*. Similar activity for *T. rhodesiense*, *T. brucei*, *T. evansi*, *T. equiperdum* and *T. equinum*.

Antrypol B.P. *Suramin*, Bayer 205, *Germanin*, Fournau 309, *Moranyl*, *Naganol*.

Urea of acid dimeta-aminobenzoyl-meta-aminoethyl-benzoyl-1-naphthylamino-4-6-8 trisulphonate of soda.

Trypanosomiasis (*T. gambiense* and *T. rhodesiense*). Loiasis, Onchocerciasis.

Intravenous, or rarely intramuscular, 1–3 grm. (15–45 gr.). Active in early stages of trypanosomiasis. (*See p. 112.*)

Aralis (Winthrop).

Tablets containing 75 mgm. of Aralen (chloroquine diphosphate) and 250 mgm. of Milibis (bismuth glycolylarsanilate).

The quantities are chosen to give a balanced therapeutic action in both prophylactic and therapeutic treatment of amœbiasis.

Intestinal and extra-intestinal amœbiasis.

Dose. Tab. 6 daily for 7 days.

Prophylactic, 3 tablets daily on 2 days a week.

Arsenamides. *Sodium thiocetarsamide.*

p-p(bis-(carboxy-methyl-mercapto)arsino) benzamide.

Filariasis. *Wuchereria bancrofti*. var. *papillipes*.

Intravenous, in 2% solution, 1 mgm. per kg. daily for 15 days. (*See p. 753.*)

Ascabiol. Contains 25% benzyl benzoate in emulsion. *Benzevan* and *Proscabin* are similar preparations.

Benzyl benzoate.

Scabies, Pediculosis (*P. capitis* and *P. pubis*).

Local application.

Auremetine.

Combination of the periodides of emetine and auramine, containing 28% emetine, 16% auramins and 56% iodine.

Amœbiasis in chronic stage.

Oral, 0.12–0.2 grm. (2–3 gr.).

Aureomycin. *Chlortetracycline.*

Antibiotic derived from Streptomyces aureofaciens.

Effective against numerous Gram-positive and Gram-negative organisms. Undulant fevers, Typhus, Q fever, Lymphogranuloma venereum, Psittacosis, Amœbiasis, Yaws, Coccidioidomycosis.

Daily doses—oral—6 mgm. per kg. in capsules of 250 mgm. three times daily for 5 days.

Intravenous or intramuscular 3 mgm. per kg. (See p. 218).

Avomine. *8-chloro-theophyllinate of promethazine.*

Nausea, travel sickness, Cholera.

Oral, tab. 25 mgm. (0.37 gr.). (See p. 443.)

Azacrin. *Amino-aza-acridine.*

2-methoxy-6-chloro-9-(5'-diethyl-amino-2-pentyl)-amino-3-aza-acridine dihydrochloride.

Tapeworm. *T. saginata* and *T. solium*.

Light diet for one day, saline laxative at night, enema next morning.

0.1 grm. phenobarbitone to reduce nausea and vomiting.

Azacrin 100 mgm.—2 given every 5 mins. with 0.6 grm. sodii bicarb.

Children, total dose 200 mgm. Adults, maximum 700 mgm.

Two hours later saline purgative. 15 cases complete worm in 30-45 mins.

Malaria.

Oral, Tab. 0.4 grm. for 5 days.

Bacitracin.

An antibiotic obtained from strains of *Bacillus subtilis*, not destroyed by blood, pus, or penicillinase. Indicated in Amœbic Dysentery. Topical application in sterile saline or as an ointment.

Oral, 80,000 units for 10 days. Intramuscular, 50,000 units for 7 days. Intravenous injection contra-indicated.

BAL (See Dimercaprol and Mel. B.)**Berberine sulphate B.P.** *Orisol.*

Oriental sore.

Subcutaneous or as ointment, 0.06-0.3 grm. (1-5 gr.).

Bismuth oxychloride.

Yaws.

Lupus erythematosus (in 10% ointment).

Oral, 0.6-2 grm. (9.2-30.8 gr.).

Camoform. *Biallylamicol, S.N. 6771, P.A.A. 701.*

6 : 6'-diallyl-a, a' bis (diethylamino)-4 : 4'-bi-0-cresol.

Allied to camoquine, readily absorbed from the intestinal tract and retained for a long time in the tissues.

Amœbiasis.

Oral, tab. 2 grm. (30.8 gr.) daily for 10-14 days.

Camoquine. *Amodiaquin, Miaquin, CAM—AQ1, S.N. 10751.*

Malaria.

Oral, 0.2 grm. of base as bihydrochloride. Adults 0.6 grm., children 0.4 grm., under five 0.2 grm.

Captostibone (*sodium 2-(carboxymethyl mercapto) benzene stibonate*).

Leishmaniasis, Chagas' Disease (*Trypanosoma cruzi*). Intramuscular 1.6 to 7 mgm./kgm. every other day for 10 days (total 3 grm. for adult).

Carbarsonum, B.P. *Amebevan, Amibiarsen, Leucarsone.*

4-carbamino-phenylarsenic acid.

Yaws, Amœbiasis.

Oral, 0.25 grm. (4 gr.) or per rectum, 2 grm. (30 gr.). (See p. 479.)

Carbonei Tetrachloridum, B.P. *Tetrachlormethane, Tetraform, C Cl₄.*

Effective anthelmintic for *Ascaris*, *Ancylostomes* and Tapeworms.

Now largely replaced by Tetrachlorethylene.

Oral. In gelatin capsules, 3 ml. (48.6 min.) maximum dosage.

Chenopodium Oil, B.P. *Oil of American Wormseed.*

Oil distilled with steam from fresh flowering and fruiting plants of *Chenopodium ambrosioides* var. *anthelminticum*. Contains 65% W/W of ascaridole.

Ascariasis, Ancylostomiasis.

Oral, 0.2–1 ml. (3–17 min.). (See pp. 789, 796.)

Chiniofon B.P. *Anayodin, Dysentulin, Quiniosulphan, Quinoxyl, Yatren.*

Sodium-7-iodo-8-hydroxy-quinoline-5-sulphonate.

Amoebiasis, Bacillary Dysentery. *Isospora hominis*.

Oral, 0.08–0.5 gm. (1–7½ gr.). Per rectum, retention enemata 2½–3% solution, 1–5 gm. (15–45 gr.). (See p. 478.)

Chloromycetin. *Chloramphenicol B.P. Add.*

Antibiotic isolated from *Streptomyces venezuelae* and *S. omiyensis* from soil.

D-(-)-threo-2-Dichloroacetamido-1-p-1-nitrophenyl-1:3 propanediol.

Typhus fevers, especially Mite typhus, Typhoid, Bartonellosis, Whooping cough, Gonorrhoea.

Intramuscular or intravenous injections 1–5 gm. (15.4–77.1 gr.) daily. (See p. 218.)

Oral, capsules 750 mgm. four times daily for 6 days. May produce aplastic anaemia, agranulocytosis and thrombocytopenic purpura.

Chloromycetin Palmilate Suspension (P.D. & Co.).

Bitterless derivative for treatment of infants and children.

Chloroquine. *Aralen, Resochin, Nivaquine, Tanakan, Avlochlor* (I.C.I.). *S.N. 7618, 3377 R.P., Chloroquin A.C.* (Winthrop-Stearne). *7-Chloro-4-(4 diethyl-amino-1-methylbutyl-amino) quinoline diphosphate-quinoline.*

Malaria (powerful schizonticide), Hepatic Amoebiasis. *Hymenolepis nana*, Balantidiasis (giardiasis). (See p. 77, Clonorchiasis, Paragonimiasis.)

Skin Diseases—discoid and subacute lupus erythematous rosacea, localized scleroderma, solar dermatitis, lymphocytosis of the face, acne; occasionally sarcoidosis, rheumatoid arthritis.

Oral.

Suppressive. 0.3 gramme once a week.

Injection, ampoules of 5 ml. (equivalent to 40 mgm. of base).

Care must be taken in children. Death reported from intramuscular injections of over-dosage in Ghana (100 mgm. to children 5–17 months).

Curative. First day 3 doses each 0.3 gramme followed by one dose of 0.3 gramme daily for 3 days. Dosage in terms of base. Side-effects—pruritis of hands.

Toxic effects. Bleaching of the hair, partial or complete. Interferes with metabolism of hexokinase. Causes dry eruptions, occasionally severe exfoliative dermatitis.

Citrinin (Lejeune, 1957).

Antibiotic made from *Penicillium thomii*.

Ulcer tropicum, Tropical ulcer. 0.5 gm. citrinin, bipotassium phosphate 0.873 gm. with 100 ml. of water.

Compound 6257. (Ciba). *Formocibazol.*

Condensation product of sulphathiazole and formaldehyde.

Cholera.

Oral, 6 gm. Total dosage 28 gm. Rectal administration advised. (See p. 442.)

Conteben. *Thiacetazonum, Thiosemicarbazone.*

(4-acetylamino benzaldehyde-thiosemicarbazone.)

Leprosy.

Oral. Powder 12.5 mgm. (1.8 gr.) to 250 mgm. (3.7 gr.).

Maximum 400 mgm. (6.1 gr.).

Course of 1 year.

Cortisone.

Cortisone acetate. Effective in remission in symptoms of rheumatoid arthritis, rheumatic fever, inflammatory eye diseases, Addison's disease, asthma, especially Blackwater Fever, sprue and elephantiasis (see p. 748).

Oral. Tab. 25 mgm. (For dosage see text).

Cortisone Ointment. Cortef. *Hydrocortisone acetate* 2·5%.

Seborrhœa. Allergic reactions due to fungus infection of feet (athlete's foot).

Crystal Violet B.P. *Gentian Violet*, *Methyl-rosaniline chloride*. U.S.P.

Hexamethylpararosanine hydrochloride.

Oxyuriasis, Cestodiasis (*Hymenolepis nana*), Clonorchiasis.

Oral, 18 mgm. per kilo for 10–20 days. Total dosage in clonorchiasis 1·2 gm.; in oxyuriasis 0·5 gm. t.d.s. for 7 days.

Cycloserine

Antibiotic from *Streptomyces orchidaceæ*.

Leprosy, Tuberculosis.

(Pardo Costello, 1958.)

Water-soluble oral capsules, 0·5–1 gm. daily.

Dapsonum B.P.C. Supp. *D.D.S.*, *Avlosulphon*, *D.A.D.P.S.*

4 : 4' *Diamino-diphenyl sulphone*.

Leprosy, Mycetoma, Nocardiasis. Dermatitis herpetiformis.

Oral. Tab. 100 mgm. (1·5 gr.) twice weekly. (See p. 555.)

Darachlor (B.W.)

Anti-malarial Tab, 15 mgm. Contains pyrimethamine and chloroquine sulphate. Rapidly-acting schizonticide.

Daraprim. *Pyrimethamine*, *Malocide* (Fr.).

5 (*p*-chlorophenyl)-2 : 4-diamino-6-ethylpyrimidine.

Malaria, especially benign tertian, Toxoplasmosis.

Oral, 10–20 mgm. or more daily; 5 mgm. daily suppressant.

Decamethylene. (Austin, 1957).

Decamethylene bis (4-aminoguanidinium iodide).

Active against *Trypanosoma rhodesiense*; see Prothidium, p. 878).

Diamino-Diphenoxy-Heptamines

Derivatives of diaminodiphenoxy heptones and hexachlorethanes. A series of drugs used successfully by Russians in the treatment of *Clonorchis sinensis* and other species of the opisthorchis group.

Diamino Diphenyl Sulphoxide. *D.D.S.O.*

Leprosy.

Acts like DDS—better in some cases.

Diamox. *Acetazolamide*.

Sickle-cell Anæmia (Hilkovitz, 1957). (See p. 28.)

Diasone. *Promanide*.

4 : 4-diaminodiphenyl sulphone disodium formaldehyde sulphonylate. (Derivative of diaminodiphenyl sulphone.)

Leprosy, Tuberculosis.

Oral or intravenous. Daily doses up to 2 grammes. (See p. 555.)

Dibistin (Ciba).

Sugar-coated tablets containing 0·05 gm. (0·7 gr.) antistin and 0·025 gm. (0·37 gr.) pyribenzamine.

A cream is also made for local application.

Has an antihistamine effect in seasonal allergic conditions, solar dermatitis, pruritic dermatitis, hay fever, etc.

Dicophanum B.P. Add. *D.D.T.*

1 : 1 : 1-Trichloro-2 : 2-di-*p*-chlorophenylethane.

Chronic poisoning arises from inhalation of dust or absorption through the skin.

Causes loss of appetite, muscular weakness and fine tremors.

Insecticide and larvicide. For quick "knock down" pyrethrum is added to dicophane spray solutions. (See p. 855.)

Dihydrostreptomycinum B.P. Add.

Consists of the hydrochloride or the sulphate.

May be given to patients who have become sensitized to streptomycin.

Causes more vestibular damage than parent substance. Streptomycin is toxic to the vestibular branch of the 8th cranial nerve.

Dimercaprol B.P. *Synonym BAL* (British Anti-lewisite).

Indicated in metallic intoxication due to heavy metals: gold, arsenic, mercury, antimony and bismuth. Compounds effective against trypanosomes and spirochaetes are divided into two groups according as to whether or not they are inhibited by BAL. Those which are inhibited are metal-containing compounds, but this property is not exercised in respect of anti-bacterial action. BAL inhibition of toxicity towards the parasite does not depend upon the same mechanism as BAL inhibition of toxicity towards the host.

Dosage. Issued in ampoules containing 100 mgm. of active substance. The following dosage by intramuscular injection into the glutei: 1st day, 100 mgm. 4 times at 4-hourly intervals; 2nd, 3rd and 4th days, 100 mgm. morning and evening; 5th and 6th days, 100 mgm. daily.

Diodoquin.

Diiodohydroxyquinoline, Dihaloquin, Embequin, Savorquin.

Contains 63·9% iodine.

Chronic Amœbiasis.

Oral, tablets 0·25 or 0·3 grm. (4 gr.), 3–10 daily for 10 days, especially for sterilizing cyst carrier cases. (*See p. 479.*)

Diphenan B.P. *Butolan, Orylan.* U.S.P.

p-benzylphenylcarbamate.

Oxyuriasis.

Oral, 0·5 grm. (7½ gr.) three times daily.

Diphétarson. *Bemarsal.*

Intestinal amœbiasis and, when combined with chloroquine diphosphate, has given satisfactory results in malaria.

Oral. Tab. Bemarsal, 2 grm. (30·8 gr.) with chloroquine 0·3 grm. (4·6 gr.) for 10 days.

Dithranol B.P. *Anthralin, Anthrarobin, Cignolin, Derobin.*

1 : 8-dihydroxyanthranol.

Oriental sore, Ringworm skin affections.

As an ointment, 0·25–3%. (*See p. 163.*)

D.M.P. Dimethylphthalas, B.P.C.

Repellent for insects, mosquitoes, tick, fleas and especially mites,

Trombicula akamushi and other mite vectors of scrub typhus.

Clothing impregnated, but should not be used on artificial silks.

D.I.M.P. cream containing 35% D.M.P. repellent.

Emetine and Bismuth Iodide B.P., *E.B.I.*

Bismuth iodide of emetine.

Amœbiasis.

Oral, 0·12–0·2 grm. (2–3 gr.). Total 20–30 gr.

In gelatin capsules for chronic intestinal amœbiasis. (*See p. 476.*)

Emetine Hydrochloride B.P.

(Emetol is a solution of emetine base in olive oil.)

Amœbiasis.

Subcutaneous or intramuscular, 0·06 grm. (1 gr.), usually given in daily doses.

Total 6–12 gr. Has powerful effect on acute symptoms, but does not cure the chronic infection or prevent "carriers."

Entacyl (B.D.H.).*Piperazine adipate.*

Ascaris lumbricoides, Trichuris trichiura, Heterophyes heterophyes in Egypt (Nagaty & Khalil).

Oxyuris vermicularis (thread worm).

Oral. Tab. 300 mgm. (4·6 gr.) 2 tab. three times daily. One tablet for each year of life. Children over six same dose as adults for oxyuris continue for 7 days.

In syrup form for children.

Entamide. R.D. 3803.*Dichloracet-4-hydroxy-N-methylanilide.*Amoebiasis. Active against *E. histolytica* 1:10,000,000.

Oral, tab. 12 mgm. per kg. for 10 days.

Enterovioform (Ciba).*Iodochlorohydroxyquinoline with sapamine.*

Infantile summer diarrhoea colitis and amoebic dysentery.

Oral. Capsules 0·75 to 1 grm. (11·5–15·4 gr.) in divided doses of 0·25 grm. for 10 days.

Erythromycin.*Antibiotic from Streptomyces erythreus.**Ilotycin, Erythrocin, Erythromycin stearate.*

Amoebiasis, Toxoplasmosis.

Oral, capsules. Dosage 300 mgm. four times daily.

Etisul or E. Tip.*Diethyl dithiol-isophthalate.*

Leprosy.

Reduces bacterial index (Davey). By inunction, percutaneous cream for inunction: in packs containing 5 grm. (See p. 557.)

Folic Acid. Pteroylglutamic acid.Synthetic product resembling *Lactobacillus casei* factor of liver and yeast

Produces hæmopoietic response in macrocytic anæmia.

Tropical sprue, Nutritional Tropical Macrocytic Anæmia.

Oral, 5–30 mgm. (See p. 519.)

Fouadin. (See Stibophen.)**Fumagillin. Antibiotic isolated from Aspergillus fumigatus.**Amoebic dysentery. Active on cultures of *E. histolytica* 1:10 million.

Oral, 50–125 mgm. per kg.

Furacin. (Evans and colleagues, 1957.)

Nitrofurazone, 5-nitro-2-furaldehyde semi carbazone.

Trypanosomiasis—*T. gambiense* orally readily absorbed by blood and C.S.F.

Oral, 2·1 to 12·5 mg./kg. t.i.d. 7–36 days. Combination with Lomidine (Pentamidine isethionate) more effective.

Gammexane.*Gamma isomer of Benzene hexachloride: insecticide.*Oral, Oxyuriasis (under trial). Ointment, $\frac{1}{2}$ per cent. Scabies.**Grisovin (Griseofulvin): Fulcin (I.C.I.) in tablet form. 0·25 grm. in doses of 1·5–2 grm. daily for 17 days, contain new antibiotic for fungous skin diseases. (See pp. 663, 665, 667.)****Guanimycin.***Mixture of Streptomycin and Sulphaguanidine. Streptomycin 5 grm., sulphaguanidine 3 grm. (46·2 gr.) per fluid ounce in suspending agent. Add 1½ fl. oz. (45 ml.) of cold water and shake.*

Bacillary dysenteries and diarrhoea.

Suspension. Oral, two tablespoonfuls every four hours—children one tablespoonful every three hours.

Hetrazan (84 L.). Banocide, Notezine, Diethylcarbamazine, citrate. U.S.P.*1-diethylcarbamyl-4-methyl piperazine hydrochloride, Hetrazan citrate.*Filariasis (*W. bancrofti*, *W. bancrofti bancrofti* Var. *pacifica*, *Loa loa*, *Onchocerca volvulus*, *Mansonella ozzardi* and *Dipetalonema perstans*). Larva migrans, *Ascaris lumbricoides*, Tropical eosinophilia.

Oral, 0·5–2 mgm. per kg. body-weight three times daily.

Hexylresorcinol, B.P. Caprokol.

1 : 3-dihydroxy-4-hexylbenzene.

Ascariasis, Ancylostomiasis, Oxyuriasis, Trichuriasis.

Oral; also 1 in 2,000 solution rectal enema for oxyuriasis. Pills of 0.2 grm (3 gr.) 5 daily. (See p. 797.)

Hydroxystilbamidine Isethionate.

2-hydroxy-4 : 4'-diamidinostilbene di-(B-hydroxyethanesulphonate).

Kala-azar, particularly antimony resistant cases, Blastomycosis, *Candida albicans* infections, and other systemic fungal infections. Palliative for myelomatosis.

Intravenous, 3-5 mgm. per kg. adult dose 250 mgm. in 10 ml. water injected slowly daily, or on alternate days.

Injection of Bismuth Salicylate B.P.C. Bisantol, Bismosan.

10% suspension of bismuth salicylate in neutral vegetable oil.

Yaws, Syphilis.

Oral. Tab. 0.6-2 grm. (9-30.8 gr.).

Deep intramuscular or deep subcutaneous, 2 ml. (32.4 min.) 60-200 mgm. (1 ml. = 0.051 grm. Bi) 0.9-3 min. (See p. 580.)

Isoniazid. Isonicotinic acid hydrazide, Nicetal, Nydrasid, I.N.H. (International Symbol).

Derivative of iso-nicotinic acid.

Leprosy, Tuberculosis.

In combination with dapsone. (See p. 870.)

Oral, tab. 6-8 mgm. per kg. Tab. and capsules 50 mgm. (0.77 gr.).

Kaolin Leve B.P. Light kaolin. Bolus alba.

Cholera.

Oral, 200 grm. in 400 ml. of water.

Mist Kaolini et Morphinae. Light kaolin 30 gr., sodi bicarb. 10 gr., tinct. chloroformi et morphinae 10 min., water to $\frac{1}{2}$ oz.

Kousso. Cusso.

Kusotorin, active principle. Dried female flowers of *Brayera anthelmintica*.

Cestodiasis, *T. saginata*, in Abyssinia.

Oral "Koussein." 1-4 grm. (15-60 gr.) in divided doses at half-hour interval. Total dosage 4-8 grm. (60-120 gr.) followed by purgative. Effective if freshly prepared. (See p. 803.)

Lapaquin (I.C.I.)

Chloroquine phosphate 250 mgm. and chlorproguanil hydrochloride 20 mgm.

Malaria. Mass prophylaxis.

Lapudrine (I.C.I.).

3 : 4-dichlorophenyl-isopropylidguanidine hydrochloride.

Oral, tablet exerts action on malaria parasites.

Malaria. Tab. 20 mgm. Prophylaxis resembles that of paludrine, but is more persistent.

Lederkyn (Lederle).

Sulpha-methrozy-pyridazene.

Sulphonamide. Shigellosis, Salmonellosis 0.5 grm. Dose 2 tabs. *statim*. Subsequently 1 tab. daily.

Magnamycin. Carbomycin.

Antibiotic derived from *Streptomyces halstedii*. Possesses amoebicidal action *in vitro*.

Amoebiasis, Toxoplasmosis.

Oral. Capsules 1-2 grm. (15.4-30.8 gr.) daily for 6-10 days.

Dosis therapeutica 40-50 mgm. per kg.

Male Fern, B.P. Filix mas.

Ether extract of dried rhizome and leaf bases of *Dryopteris filix mas* containing 25% W/W filicin.

Cestodiasis.

Oral, 3-5.5 ml. (60-90 min.) in gelatin capsules followed by saline aperient. (See p. 801.)

Mandelic Acid B.P.C.

α-hydroxy phenylacetic acid, phenylglycollic acid.

Urinary infections, especially *Bact. coli*.

Oral in syrup, 2-4 grm. (30-60 gr.).

Mantomide. *Win.* 5047.

N (2,4-dichlorobenzyl)-*N*-(2 hydroxy-ethyl) dichloroacetamide.

Amoebiasis. Active against *E. histolytica* 1:1,000,000. Oral—under 5 years, 250 mgm. (3·7 gr.) taken daily for 8 days; 5-10 years, 500 mgm. (7·7 gr.) t.d. for 10 days; over 10 years, 750 mgm. (11·5 gr.) t.d. for 10 days.

Melarsen (Friedheim). Sodium salt of *p*-melaminylphenylarsonic acid, syn. triazine arsonic acid, compound 4289. Pentavalent arsenical.

Effective in first and second stage, including trypanamide resistant sleeping sickness (trypanosomiasis) 12 i.m. or i.v. injections of max. 0·02 g./kg. each at 5 days interval. Ceiling 2·0 g.

Melarsen oxide (Friedheim). *P*-melaminylphenylarsenoxide. Trivalent derivative of Melarsen.

Effective in first and second stage and trypanamide resistant sleeping sickness. 5% solution in propylenglycol to be injected i.v. Two series of 7 daily injections of 1·5 mgr./kgm., the two series separated by a rest period of one month; or one series of 15 injections of 0·5 mgr./kg., every second day.

Melarsen-sodium.

Monosodium salt of p-(2 : 4-diamino-1 : 3 : 5-triazinyl-6)-aminophenyl-arsonic acid.

A pentavalent arsenical compound.

Trypanosomiasis, due to *T. gambiense*, especially for late relapsing trypanamide resistant cases.

Intravenous. Freshly prepared 10% solution.

Adults 1 grm. (15·4 gr.) adolescents 0·7 grm. (10·8 gr.) children under twelve 0·4 grm. (6·1 gr.) 8-12 injections at intervals of 5-7 days.

Mel. B (Friedheim). *P*-melaminylphenylarsenoxide-2,3-dimercapto-propanol. Syn. Arsobal, Melarsoprol.

Trivalent arsenical derived from Melarsenoxide by condensation with BAL. Active in all stages of *T. gambiense* and *T. rhodesiense* sleeping sickness.

3·6% solution in propylenglycol.

One or two series of 3 to 4 i.v. daily injections of 3·6 mgr./kg., a week interval between series.

Mel. W (Friedheim).

A new allied compound for *W. bancrofti* filariasis.

Intravenous in doses of 0·1, 0·2, 0·2 grm. on 3 days. It is claimed that adult *W. bancrofti* are killed (de Jongh, 1959).

Mepacrine hydrochloride B.P. *Atabrine, Atebrin, Acricquine, Chemiochin, Chinacrin, Crinodora, Erion, Italcina, Malacicide, Quinacrine, Meloquine.* 2-chloro-5 (4-diethyl-amino-*i*-methylbutylamino)-7-methoxyacridine dihydrochloride dihydrate.

Malaria, Giardiasis, Cestodiasis, Oriental Sore, Lupus erythematosus, Rheumatoid arthritis.

Oral, 0·05-0·1 grm. ($\frac{1}{2}$ -1 $\frac{1}{2}$ gr.) initial dose as high as 0·2-0·3 grm. (See p. 79.)

Mepacrine methane-sulphonate B.P. *Atebrin musonate, Quinacrine soluble.*

Dimethanesulphonate of mepacrine.

Malaria, Giardiasis.

Intramuscular or subcutaneous, 0·05-0·1 grm. ($\frac{1}{2}$ -1 $\frac{1}{2}$ gr.). (See p. 80.)

Milibis. *Wia.*

Bismuth derivative of oxy-para-N-glycolyl-arsanilate. Contains 15·01% arsenic: 41·81% bismuth.

Amoebic Dysentery.

Oral, tablets 250 mgm. three times daily 7-16 days. (See p. 479.)

Miracil D. *Nilodin, Thiozanthone, Tizantone.* Lucanthone hydrochloride. B.P.

Hydrochloride of 1-methyl-4-beta-diethyl-aminoethyl, aminothiozanthone.

Schistosomiasis, *S. haematobium*.

Oral, 300 mgm. at twelve hour intervals up to 14 days. (See p. 701.)

Mycil (B.D.H.).

Mycil ointment, dusting powder, contains fungicide—*chlorophenesin*.

Mycil pessaries contain chlorophenesin and *D.M. 238 (hydroxy dichloro-diphenyl-methane)*.

Fungicidal preparation.

Fungous infection of feet, *Tinea circinata*, *T. cruris*, *T. unguium*.

Mycostatin. Nystatin.

Antibiotic originally named fungicidin.

Coccidioidomycosis.

Has been shown to be fungistatic to cultures of *Coccidioides immitis*.

Neoarsphenamine B.P. Neoarsaminol, Neo-arsenobenzolum, Neoarsenphenolamine, Neo-diarsenol, Neosalvarsan (Ehrlich 914), Novarsan, Novarsenobenzene, Novarsenbenzol, Novarsenobillon, N.A.B., Novostab, Rhodarsan.

Sodium 3 : 3'-diamino-4 : 4'-dihydroxy arsenobenzene-N-methylene sulphonylate.

Relapsing fever (*S. duttoni* and *S. recurrentis*), Rat-bite fever (*S. minus*), Yaws,

Syphilis, Malaria, Kala-azar, Trypanosomiasis, Tropical Eosinophilia.

Intravenous, 0.15-0.9 gm. (2.3-13.8 gr.).

Neo-hepatex.

Proteolysed extract of liver for parenteral use. Contains also vitamin B₁₂ in excess of 12 μ . (microgramme) per ml.

Tropical Sprue, Nutritional tropical megalocytic anaemia, malarial anaemia.

Intramuscular 2 ml. (32.4 mins.) on alternate days.

Neomycin.

Antibiotic obtained from *Bacillus fradiae*.

Consists of three antibiotics known as neomycin complex.

It is a good intestinal antiseptic and has been used successfully in the treatment of Gram-negative urinary tract infections. Neomycin contains a nephrotoxic factor.

Neostam. Stibamine glucoside.

Nitrogen-glucoside of sodium p-aminophenylstibonate.

Kala-azar, Oriental Sore, Espundia.

Intravenous, 0.2 gm. (3.2 gr.), repeated as regular intervals. (See p. 163.)

Neostibosan. Bayer 893B, von Heyden 893.

Diethylamine-p-aminophenyl-stibinate.

Kala-azar, Oriental sore, Espundia.

Intravenous or intramuscular, 0.2 gm. (3 gr.). (See p. 163.)

Nicotamidum B.P. Nicotinic acid amide.

Pyridine-3-carboxylic acid amide.

Pellagra.

Oral, tablet 50-250 mgm. (0.77-3.85 gr.) daily.

Nicotinic acid B.P. Niacin.

Pyridine-3-carboxylic acid.

Pellagra.

Oral, tablet 50-250 mgm. daily; also intravenous.

Nivaquine (M. & B.) is the trade name for Chloroquine sulphate. Nivaquine (chloroquine sulphate) is known as Nivaquine B in U.S.A. Nivaquine C is 3-methyl-4 (diethylamino-pentyl) amino-7-chloroquinoline dihydrochloride which also is active against all forms of malaria, but is not procurable in Great Britain.

Nivembin (M. & B.).

Chloroquine-di-iodohydroxy-quinoline tablets, each containing chloroquine sulphate 65 mgm. and di-iodohydroxy-quinoline 300 mgm.

Amoebiasis and amoebic hepatitis.

Oral, tab. one three times daily.

Nor-adrenalin (*Levoped*).

12-amino-1 (3,4 dihydroxyphenyl) ethanol. Differs from adrenalin by absence of methyl substitution in the amino group formula.

Used in restoration of circulation in peripheral vascular failure in cerebral malaria.

Novex.

(22" dihydroxy 55") (*dichloro diphenyl sulphide*.)

D.D.S. and Novex should be given extended trial in mycetoma preliminary to surgery (see p. 591).

Novobiocin. *Albamycin, Cathomycin, Biotexin* (Glaxo).

Antibiotic isolated from *Streptomyces niveus* or *Actinomyces*.

Identical with "cathomycin" and "cardelmycin" (*crystalline acid*).

Effective against a number of Gram-negative organisms and inhibits the growth of gram-positive cocci and undulant fever (*Br. melitensis*).

Oral, capsules 0.125–0.500 grm.: then 6 hourly up to 18 grm.

Oleoresin of Aspidium.

Contains *filicin*.

Costodiasis and *Heterophyes heterophyes*.

Oral, —3₁ (3.75 ml.) in emulsion. (See p. 977.)

Paludrine (4888). *Proguanil, Chlorguanide, Diguanil, B.P., Guanatol, Drinupal, Palusil Trian, Chloriguane, S.N. 12837.*

N,1-*p*-chlorophenyl-*N*₈-isopropylbiguanide acetate, lactate, and monohydrochloride.

Malaria, all forms.

Oral, 0.1–0.75 grm. (1.5–11.5 gr.) daily, 7–10 days. Prophylactic, 0.1 grm. (1.5 gr.)

Pamaquine, B.P. *Beprochin, Plasmochin, Plasmoquine (simplex), Præquine, Gamefar, Quipenyl, Aminoguin.* (6-methoxy-8 (4-diethylamino-1-methylbutylamino) quinoline).

Malaria, gametocide, and in antirelapse treatment in subtertian.

Oral, 0.02–0.04 grm. (0.3–0.6 gr.) daily for 7 days. (See p. 78.)

Paromomycin.

Broad-spectrum antibiotic. *In vitro* equals tetracycline, erythromycin, and neomycin.

In all bacterial diseases, plague, undulant fevers.

Oral, capsules 8.4 grm. over 7–14 days.

Penicillin B.P.

The sodium potassium or calcium salt from *Penicillium notatum*. Procaine penicillin has more lasting effect (0.3–0.6 mega units daily). Penicillin aluminium monostearate (P.A.M.) recommended by W.H.O. for Yaws. *Bicillin* effective for 2 weeks (*N,N'*-dibenzyl ethylene diamine, dipenicillin G.), also Penicillin G. (*Neopenil*) diethylaminooethyl ester hydriodide.

Staphylococcal, streptococcal, gonococcal, pneumococcal, and other gram-positive infections, and for the treatment of Syphilis, Yaws, Ulcus Tropicum, Relapsing Fevers, Leptospirosis, Rat bite fever, and megalocytic anaemia.

Intramuscular injection, 1 mega unit twice daily. Calcium salts used by mouth and for topical application.

Pentamidine isethionas B.P.C. (M. & B. 800).

4 : 4-diamidino-diphenoxy-pentane di-(β -hydroxethane sulphonate). Lomidine (*Fr.*) is pentamidine dimethanesulphonate. In these compounds 1 mgm. of base equals, 1.21 mgm. of the dihydrochloride; 1.74 mgm. of the di-isethionate; and 1.56 mgm. of dimethane sulphonate (lomidine). (See p. 115.)

Trypanosomiasis, Kala-azar, Espundia.

Intramuscular, 4 mgm. per kg. body-weight dissolved in 3–4 ml. of water. Injections can be given daily or on alternate days. A course consists of not less than 12 injections. May also be given intravenously, but this is frequently followed by a rapid fall in blood-pressure with sometimes the alarming symptoms of collapse. For the prophylaxis of trypanosomiasis 175 mgm. are given at six months' intervals. In ampoules of 200 mgm. (3 gr.); containers of powder each of 2 grm. (30.8 gr.).

Phenergan.*Promethazine hydrochloride.*

Potent antihistamine for allergic conditions, filariasis and schistosomiasis; also has sedative and hypnotic properties.

Oral. Tab. 25 mgm. and 10 mgm. Injection, 2·5 per cent. solution. Topical, 2 per cent. cream.

Phenothiazine. Phenovis.*Thiodiphenylamine.*

Ascariasis, Oxyuriasis, Dracontiasis.

Oral, 4–8 grm. (60–120 gr.) spaced over 4 days. May be dangerously toxic in children.

Injected in oily solution in 1 grm. doses in vicinity of guinea-worm.

Phthaliylsulphathiazole. Thalistatin, Thalazole.

Bacillary dysentery, Ulcerative colitis, Infantile gastroenteritis, Chronic amoebic dysentery, Pre- and post-operative use in intestinal and rectal surgery.

Oral. Average adult dose in bacillary dysentery 3–4 grammes daily. Much higher doses used in surgery.

Piperazina. Piperazine hydrate. Antepar Elixir (B. W. & Co.)

Oxyuriasis, Ascariasis, especially in children.

In syrup 50–75 mgm. (0·7–1·37 gr.) per kg. per day, $\frac{1}{2}$ gr. (0·008 grm.) daily per year of life.

(See also Entacyl.)

Poly (Methylene-4-hydroxy-benzene arsonic acid.)

Mixture of formaldehyde and 4-hydroxy-benzene arsonic acid.

Amoebiasis.

Tab. adults 500 mgm. t.d.s. 7–10 days (Hoekenga, 1957). 80% satisfied criteria of apparent cure.

Polymyxin.

A generic term for an antibiotic mixture, produced from *Bacillus polymyxa*. It has been shown to have at least four antibiotics—polymyxin, a, b, c, d.

Polymyxin b is of most value. It is highly active against Gram-negative bacteria.

Prednisone, Prednisolone Decortisyl (Roussel).

Oral. Tab. 1 mgm. and 5 mgm. cortisone derivatives.

Blackwater Fever (see p. 63).

Primaquine Phosphate, B.P.C. Primaquinium phosphate.

8-(4-amino-1-methyl butylamino)-6-methoxyquinoline di(dihydrogen phosphate), allied to pamaquine.

Malaria, especially benign tertian. Prevents relapses, particularly when combined with quinine.

Oral, tab. 10–15 mgm. base for 14 days, or 7 mgm. three times daily for 14 days.

Promanide. Prominin, U.S.A.

Sodium 4 : 4'-diaminodiphenyl sulphone, N-N'-dextrose sulphonate.

Leprosy, Tuberculosis.

Intravenous 1–5 grm. (15·4–77·1 gr.) daily: increase gradually.

Can be continued for long periods. May produce severe hæmolytic anæmia.

Promizole.

4 : 2-diaminophenyl-5-thiazolyl phenyl sulphone.

Leprosy, Tuberculosis.

Oral, daily doses up to 6 grammes.

Propamidine isethionate.

Trypanosomiasis (*T. gambiense*).

Intramuscular, 300 mgm.—prophylactic. (See p. 117.)

Streptohydrazid.

Combination of isoniazid and streptomycin.
Leprosy (Dreisbach and Cochrane).

Streptomycini Sulphas B.P. Add.

Antibiotic isolated from *Actinomyces griseus*, employed as the sulphate.

Meso-1-3-diguanidino-2, 3, 4, 6, tetrahydroxy-cyclohexane glucoside of a disaccharide.

Active entirely against gram-negative organisms.

Tuberculosis, Plague, Tularæmia, Ulcerating Granuloma of Pudenda, "Q Fever,"

Bacillary Dysenteries, *Bact. coli* infections, Meningitis, Whooping Cough, Actinomycosis and Gonorrhœa.

Intramuscular in solution 0·5 grm. of the base daily.

Oral in cachets, 250 mgm. (3·7 gr.) four times daily, for intestinal infections taken with a cup of milk or water.

The following preparations are in use: *Streptomycin et Calc chloridum*, *Injectio Streptomycini et Calc chloridi*, *Streptomycini Hydrochloridum*, *Streptomycini sulphas* and *Injectio Streptomycini Sulphatis*.

Streptotriad. *Trisulphonamido*|*streptomycin*.

Streptomycin 65 mgm., sulphathiazole sulphate 100 mgm., sulphadiazine 100 mgm., and sulphamerazine 65 mgm.

Bacillary dysenteries, and for symptomless carriers.

Oral. Tab. adults 3 tablets t.d.s. Children 0-2 years, $\frac{1}{2}$ tablet; 2-5, 1 tablet; 5-15 years, 1½ tablets.

Adequate fluid intake should be ensured.

Stylomycin. (*Puromycin*, *Achromycin*.)

Antibiotic from *Streptomyces albo-niger*.

Active against *T. cruzi* in vivo, also in *T. equiperdum*, *T. gambiense*, *T. rhodesiense* in mice. *T. congolense* resistant especially active against *T. rhodesiense* and *T. gambiense* (Trincão).

Oral. Capsules, 250 mgm. every 12 hours for 7-14 days to total of 10-20 grm. Results in man encouraging in early and meningeal stages. (Heuls *et al*, 1958).

Succinyl-Sulphathiazole B.P. *Sulphasuxidine*, *Colistatin*.

2-(*p*-succinyl-amino benzenesulphonamido) thiazole.

Bacillary dysenteries, Ulcerative colitis.

Oral, 10-14 grm. (150-210 gr.). Initial dose 4 grm. followed by maintenance dose of 2 grm. 4 times daily. American workers advocate large doses: 0·25 grm. per kilo body-weight for pre- and post-operative treatment.

Sulphadiazine B.P.

2-(*p*-aminobenzenesulphonamido)-pyrimidine.

Pneumonia, Malaria, Plague, Filariasis, Lymphogranuloma inguinale, Melioidosis.

Oral, 1-4 grm. (15-60 gr.): initial dose 4 grm. followed by 1 grm. every four hours.

Sulphadimidine B.P. *Sulphadimethylpyrimidine*, *Sulphamezathine*.

2-(4-aminobenzenesulphonyl-amino-4 : 6-dimethylpyrimidine).

Pneumonia, Bacillary dysenteries, Ulcerative colitis.

Oral, tab. 2 grm. (30·8 gr.). Initial dose = 1 grm. (15·4 gr.). Subsequently, every 6 hours for 5-7 days.

Sulphaguanidine B.P. *p*-aminobenzenesulphonylguanidine monohydrate.

Bacillary dysenteries.

Oral, 5-20 grm. (75-300 gr.). Opinions vary on optimum dosage. Many consider dosages advocated too large. (See p. 459.)

Sulphapyridine. B.P.C. *Dagenan* (*M. & B.* 693), *Eubasinum*, *Sulphidine*.

2-(*p*-aminobenzenesulphonamido)-pyridine.

Lymphogranuloma inguinale, Madura foot, Bubonic plague, Streptococcal infections, Pneumonia, Gonorrhœa, Cerebrospinal meningitis.

Oral, 0·5-2 grm. (7½-30 gr.) followed by 1 grm. 4-hourly for 2 days. Then 1 grm. 6-hourly for 2 days.

Sulpharsphenamina B.P. *Myosalvarsan, Sulpharsenol, Sulpharsenobenzene, Sulphostab.*
Disodium-3 : 3'-diamino-4 : 4'-dihydroxyarsenobenzene-N : N'-dimethyl sulphate.

Relapsing fever, Yaws, Syphilis, Trypanosomiasis.
Intramuscular or intravenous, 0·1-0·6 gm. (1·5-9·2 gr.).

Sulphathiazolum B.P. *Thiazamide, Cibazol.*

2-(p-aminobenzenesulphonamido)-thiazole.

Pneumonia, Malaria, Plague, Filariasis, Lymphogranuloma inguinale.
Oral, tab. 2 gm. (30·8 gr.) initially; 1 gm. (15·4 gr.) every 4 hours.

Sulphatriad. (*M. & B.*)

An association of sulphathiazole 0·37 grm. (5·6 gr.), sulphadiazine 0·37 grm. (5·6 gr.)
and sulphamerazine 0·26 grm. (3·9 gr.) per grm. for systemic sulphonamide therapy
with reduced risk of crystalluria.

Oral, tab. 2-4 gm. (30·8-61·7 gr.). Course as for other active sulphonamides.

Sulphetrone.

Tetrasodium-4-4'-1-γ-phenylpropyl-amino-diphenyl sulphone tetra-sulphone.

Leprosy, Tuberculosis.

Oral, 6-9 gm. daily with an initial dose of 1·5 gm. daily and gradually increased.
(See p. 556.)

Telmid. *Dithiazanine iodide* (Eli, Lilly).

(3-ethyl-2 [5-(3-ethyl-2-benzothiazolinydene-1-3-pentadienyl) benzothiazolium iodide].

Anthelmintic for Ascaris, Strongyloides, Trichuris, Oxyuris.

Oral. Tab. 200 mgm. 10 mgm./kgm. enteric-coated (CAP). 2 tabs. 4 times daily for
5 days after meals and at bedtime.

Teropterin.

Pterolyl-γ-glutamyl-γ-glutamyl glutamic acid.

Tropical Sprue, Pernicious Anæmia.

Intramuscular injection 10-20 mgm. (0·15-0·3 gr.) daily.

Ampoules of 1 ml. containing 10 mgm. (0·15 gr.) injected daily for one week.

Terramycin. *Oxytetracycline.*

An antibiotic isolated from cultures of *Streptomyces rimosus*.

Amœbiasis, Typhus Fevers, Salmonella infections. *Bact. coli* infections. Oxyuriasis,
Balantidiasis, Ulcus Tropicum, Yaws.

2 gm. daily by mouth in divided doses, or 0·5-1 gm. daily intravenously in divided
doses. Tablets of 0·25 gm. each.

Tetrachlorethylene, B.P.

Ethylene tetrachloride.

Ancylostomiasis, Oxyuriasis, *Hymenolepis nana*.

Oral, 3 ml. (51 min.). (See p. 796.)

Tetracycline. *Achromycin, Tetracycl, Polycycline.*

A broad-spectrum antibiotic prepared by reduction from aureomycin (chlortetracycline)
(*q.v.*). Antibacterial activity similar to that of chlortetracycline and oxytetracycline
but causes fewer side-effects and is more stable.

Effective against numerous Gram-positive and Gram-negative organisms. Undulant
fevers, Typhus, Q fever, Lymphogranuloma venereum, Psittacosis, Amœbiasis, Yaws,
Coccidioidomycosis.

Oral. 250-500 mgm. 4 times daily.

Injection. Intramuscular, 200-300 mgm. daily in divided doses at 8-12 hour intervals.

Intravenous, 500 mgm. 12 hourly by drip as 0·1% solution.

Tetraethylurammonosulphide. *Tetmosal.*

Scabies.

When combined with soap in 5-20% dilution, it retains its sarcopticidal properties.

882 TABLE OF DRUGS—TROPICAL DISEASES

Thiacetazone. *Thioparamizone.*

p-cetylaminobenzaldehyde thiosemicarbazone.

Tuberculosis and leprosy.

One 5 mgm. tablet daily, gradually increased to 3 or 4 tablets daily.

Thiambutosine (Ciba).

or S.U. 1906.

Diphenyl thiourea.

(4-butyl-4'-dimethyl aminophenyl thiourea).

Leprosy, Tuberculosis.

Oral. Tab. 0.5 grm. daily for 2 weeks, increasing by 0.5 grm. every fortnight up to maximum of 4 tablets daily. Children 25-40 mgm. per kgm.

Thio-bismol.

Sodium salt of bismuth thio-glycollic acid.

Benign Tertian Malaria.

Intramuscular injection 0.2 grm. (3 gr.). (See p. 93.)

Thymol, B.P.

3-methyl-6-isopropylphenol.

Ancylostomiasis.

Oral, tab. 3-4 grm. (46.2-61.7 gr.).

Tomatin.

Antibiotic for Histoplasmosis.

Trichlorethylenum B.P.

Trilene.

Ancylostomiasis, oxyuriasis.

Oral. Liquid 2-3 ml. (32.4-48.6 min.) in capsules or mixture. Contra-indicated in heart or kidney disease.

Triostam.

Sodium antimonyl gluconate.

Trypanosomiasis:—Schistosomiasis, *S. hæmatobium* and *S. mansoni*. Six per cent. solution. Intravenous 15-20 mgm. per kg. Six-day course. Adult man 60 kg., dosage 200 mgm. for 6 days. Oral, enteric-coated tablets.

Tryparsamide B.P. *Tryparson, Tryponarsyl, Trypotan, Novaloxyl, Glyphenarsine.*

Sodium-N-phenylglycineamide-p-arsenate, Acetyl-p-amino-o-oxyphenyl arsenic acid.

Trypanosomiasis (*T. gambiense* and *T. rhodesiense*), Neurosyphilis.

Intravenous or intramuscular, 1-2 grm. (15-30 gr.). (See p. 113.)

T. W. Sb. (Friedheim).

Antimony-a-a-dimercapto succinate. See under Antimony.

Urea Stibamine. *Stiburea.*

A combination of urea and p-aminophenylstibinic acid.

Kala-azar.

Intravenous or intramuscular, 0.2 grm. (3 gr.). (See p. 151.)

Vadrine. *p. aminosalicylate of 2-pyridyl-(4)-1,3,4-oxdiazolone-(5).*

Leprosy (Jobling and Ridley).

Oral, tab. 200 mgm. 1 tab. every 6 days, up to maximum dosage of 40 mgm./kgm. body weight.

Vitamin B 12. **Cyanocobalaminum B.P.C.** *Bilevan, Cytamen, Distivit, Normocytin.*

Pernicious anæmia, Nutritional macrocytic anæmia, Tropical Sprue and Macrocytic anæmia of pregnancy.

Intramuscular injection 50 µ mgm.

APPENDIX

SECTION A.—MEDICAL ZOOLOGY

I. Medical Protozoology

PHYLUM PROTOZOA

Class: Sporozoa. Sub-class: Haemosporidia.

PLASMODIIDÆ. (Malaria Parasites.)

Genus *Plasmodium*.

The number of known species of plasmodium in man and animals is about 120. Four species occur in man: *Plasmodium vivax*, *P. ovale* (p. 888), *P. malariae* (p. 887) and *P. falciparum* (p. 889). Closely allied organisms have been found in apes and monkeys. *P. pitheci* in the orang outang (*Pongo pygmaeus*) somewhat resembles *P. malariae*. *Hepatocystis kochi* and *P. gonderi* occur in *Cercopithecus*. *P. knowlesi*, which is a commensal in *Macaca irus*, the "Kra Monkey," produces a fatal infection in 99 per cent. when inoculated into *Macaca mulatta* and is accompanied by Schüffner's dots like *P. vivax*. *P. cynomolgi*, also a parasite of *Macaca irus*, closely resembles *P. vivax*. *P. reichenowi*, which resembles *P. falciparum* and produces crescents, has been discovered in the chimpanzee and gorilla.

Human malaria has been transferred to other mammals by Taliaferro who produced transient infection with *P. falciparum* in the red howler-monkey (*Alouatta seniculus*) in South America; while Rodhain succeeded in infecting the chimpanzee with *P. vivax* by sporozoite infection and demonstrated the E.E. cycle in the liver. The erythrocytic forms can maintain themselves for a few weeks. Bray (1957) has infected the chimpanzee successfully with *P. ovale* by the bite of *A. gambiae* and has reproduced the tissue phase of *P. falciparum* in the liver as well as the erythrocytic phase of this parasite in a splenectomized animal (1958). Three common species of human malaria parasites, the benign, subtertian and quartan, are suspected to occur as natural infections of the chimpanzees.

The European mosquito, *Anopheles maculipennis atroparvus*, is an efficient carrier of *P. cynomolgi*, and, although monkeys have been successfully infected by the bites of these mosquitoes, the same batch of insects failed to produce the disease in man. Some successful inoculations of man with certain species of monkey parasites have been recorded. Knowles and Das Gupta, followed by other workers, have on many occasions infected man with *P. knowlesi*, but by direct blood inoculations only. *P. gonderi*, *P. inui* and *P. schweiz* of the chimpanzee which resembles *P. vivax* have also been passed to man.

These experiments, though few in number and relating to only four species of monkey parasite, provide scientific evidence that at least some species of parasites belonging to the lower monkeys are able to produce infection in man, at least under artificial conditions.

A number of malaria-like parasites have been described from rodents. Of these the most important are *P. berghei* from the tree rat, *Praomys jacksoni* of the Belgian Congo and *P. vinckei*, Rodhain, from *Thamnomys dasteri*. The insect vector is *Anopheles duren*. The infection is easily passed to rats, mice and to the cotton rat. In these animals it causes heavy parasitæmia and death from the eleventh to fifteenth days. Liver and spleen are greatly enlarged and, like *P. vivax*, infected red corpuscles are

grossly enlarged. Ressler has found *P. inopinatum*, a new species, in splenectomized rats and Field and Edeson *Hepatocystis vassali malayensis* in four species of squirrel (*Callosciurus*) in Malaya, while *P. brodeni* has been described from the African elephant shrew, *Elephantulus rufescens dundasi*. Birds have a number of malaria-like parasites: others have been recorded in bats and squirrels, and even lizards. *P. relictum* and *P. cathemerium* are present in sparrows and other birds. *P. lophuræ*, a parasite of Pekin ducks, has been much employed for chemotherapeutic studies. Elongated schizonts and gametocytes rather resembling *P. falciparum* are found in *P. circumflexum*. Avian intracorporeal parasites are transmitted by culicine mosquitoes, as a rule, but also by anopheles. In the avian red blood corpuscle *Plasmodium* displaces the cell nucleus, thus differing from *Hæmoproteus*, a common blood parasite of tropical finches and pigeons, which is transmitted by a hippoboscoid fly, *Lynchja maura*. An interesting side-light on the development of plasmodiids in the vertebrate host has been shed by the discovery of a plasmodium of fowls, *Plasmodium gallinaceum*,* which produces pigmentless schizonts in the endothelial cells of capillaries of the brain kidney, lung, liver, heart and bone-marrow, constituting the exoerythrocytic (E.E.) cycle, and similar stages have been found in *P. circumflexum*, *P. relictum*, *P. cathemerium* of the canary, and in *P. lophuræ* of the duck.

This is the result of studies in tissue-culture by Hawking and in chicks inoculated with sporozoites of *P. gallinaceum* from the salivary glands of *Aedes aegypti*, which transmits this parasite. They are detectable in the intercellular spaces, but soon become oval or spheroidal parasites in the macrophage cells, and the mature schizonts make their appearance from the thirty-sixth to the forty-eighth hour. When liberated they enter other macrophages and wander widely. The second generation are known as the metacryptozoites, some of which enter erythrocytes. After the second generation all organs become infected. About the fifth day a type of schizont appears which gives rise to large numbers of micromerozoites in contrast to the earlier generation with smaller numbers of macro-merozoites (Huff and Coulston, 1945).

This cycle was found for the first time in the endothelial cell in a mammal (bat) by Mer (1947) and shortly afterwards in a cercopithecus monkey (Garnham), but these latter parasites belong to a new genus, *Hepatodystis*, and are now known as *H. murinum* and *H. kochi* respectively. The E.E. cycle in the genus *Plasmodium* was first demonstrated by Shortt and Garnham in *P. cynomolgi*, and recently also in *P. knowlesi*. A pigmented cryptomerozoites have been found also in the human liver in the case of *P. vivax*, *P. falciparum*, and *P. ovale*.

Pigment-producing parasites in the blood cells of certain reptiles are either *Hæmoproteus* or *Plasmodium*.

HUMAN MALARIA (GENERAL ACCOUNT)

The four species of parasite (*Plasmodium*) causing malaria in man differ from each other in morphology, but the general course of their life-history is similar. They all have two distinct phases: intracorporeal and extracorporeal. Each

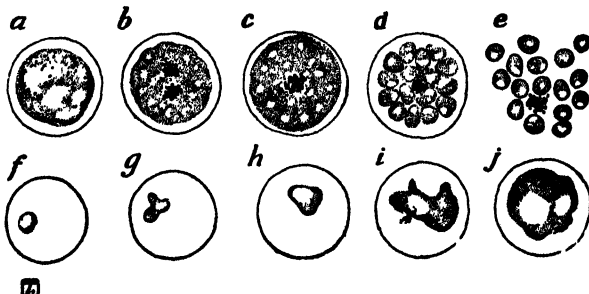


Fig. 251.—Evolution of the tertian parasite, unstained.

*Now renamed *Hæmaphysa gallinacea* (Garnham)

species has its special intracorporeal erythrocytic life-cycle that may last approximately 48 to 72 hours.

The malarial parasite can be recognized in fresh unstained malarial blood an hour or so before a paroxysm; it is a pale disc inside the red blood corpuscle (Fig. 251, *a*), and at a later stage a number of fine black or reddish-black particles of pigment (*hæmzoin*, formerly known as *melanin*) are scattered throughout its protoplasm. It collects, as the parasite grows, in central blocks round which the protoplasm becomes divided into segments (merozoites); when the cycle is complete the containing corpuscle (host cell) breaks down and liberates the merozoites, none of which contain *hæmzoin*. This stage coincides with a clinical fever.

The ring forms of subtertian malaria are very small in the acute phase but are larger in the chronic (Shute).

A number of these freed merozoites escape phagocytosis by wandering leucocytes and attach themselves to other red corpuscles, enter them, and grow at the expense of the hæmoglobin, exhibiting active amoeboid movements. When appropriately stained, the free merozoites are seen to consist of a nucleus surrounded by a ring of protoplasm; as they reach maturity a nucleolus becomes visible (Fig. 251, *a*, *j*). In the pre-sporulation phase the nuclear elements become scattered throughout the protoplasm, and around them the segmenting parasite arranges itself to form merozoites (Fig. 251, *b*, *c*). The *hæmzoin* or pigment particles of the malaria parasite are either black or dark brown dust-like specks, grains or rods, isolated or aggregated into more or less dense clumps. As long as the nucleus remains entire, the *hæmzoin* is peripheral, but when segmentation takes place it becomes central.

The number of parasites necessary to produce fever depends not so much upon their number as on the degree of tolerance on the part of the host—whether it is a first relapse, second, third and so on. Each differs enormously.

In a primary attack prolonged search may fail to reveal any parasite on the first day of fever and even on the third only 5 per c.mm. may be found, while in a long-term relapse 3,000 parasites per c.mm. may be found on the first day with numerous gametocytes.

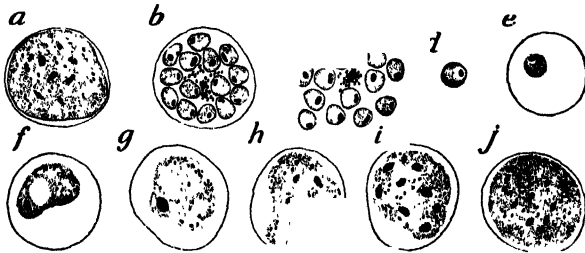


Fig. 252.—Evolution of the tertian parasite, stained.

SPOROLOGY.

The extracorporeal or mosquito stage commences with a process of exflagellation. This is a sexual phase which can only take place in the blood, after it has been withdrawn from the body. As observed in fresh wet preparations of blood the flagellated body is derived from the male sexual cells or gametocytes, which are composed of protoplasm and *hæmzoin* and which possess, on more minute examination, a distinctive structure. These sexual cells are usually round, but in subtertian malaria (*P. falciparum*) they are crescentic. These well-known "crescents" become rounded off before flagellation. The flagella (more correctly, the microgametes) number from one to six or more. They are extremely delicate

filaments, which contain chromatin and move about rapidly and which, every now and again, break away and swim about with vibratile movement. Only the male cell (microgametocyte) undergoes this process; the female (macrogametocyte) remains rounded and stationary until fertilized by one of the erupted flagella (microgametes). This event signalizes the first stage in the development of the malaria parasite in the stomach cavity of the anopheles mosquito. There sporozoites develop in the oöcyst on the external or coelomic surface of the stomach of the mosquito and later migrate to the salivary glands of this insect, gaining entrance to the bloodstream of man via the saliva. They then penetrate the hepatic cells where the pre-erythrocytic and exoerythrocytic cycles take place (see p. 895).

BENIGN TERTIAN. (*Plasmodium vivax*)
(Pl. II B, facing p. 70)

In the early stages the parasite is ring-shaped, measuring (2-4 μ) one third the diameter of the containing corpuscle. It has been shown that this parasite particularly favours reticulocytes, because they are less easily phagocytosed than older cells.

The nucleus is large, situated at the thinnest part of the ring. (It is sometimes duplicated to form two dots which represents the original structure broken into two fragments). As the ring grows, so the corpuscle enlarges and Schüffner's dots are formed. At thirty hours, the trophozoite becomes amoeboid whilst hæmoglobin is being deposited in the cytoplasm in the form of pigment. The extruded pseudopodia explain the great irregularities in the contour seen in unstained specimens (Fig. 251), but movement ceases directly the parasite has attained maximum size. The nucleus divides in thirty-six hours; the parasite may now be 10-12 μ in size and the host cell twice as big as normal, but the vacuole in which the nucleus is situated, and which is filled with chromatin, becomes smaller as the parasite develops. At 40 hours it is nearly fully matured. Schüffner's dots are chromophilic particles which stain with Romanowsky's stain. At first fine, they soon become coarse and more prominent and characteristic of *P. vivax* and *P. ovale*. Sometimes the infected red corpuscle is twice normal size, and usually the rim surrounding the parasite has a washed-out appearance.

Schizogony.—The fully formed schizont is almost round, larger than the diameter of a normal corpuscle, nearly 9 or 10 μ in diameter. The nucleus is at first fairly large, lying near the periphery, with chromatin diffusely arranged; one or two small vacuoles may be present. Multiplication proceeds by repeated division of the nucleus, followed by segmentation of the protoplasm, the result of which is a mulberry-shaped mass. The number of merozoites thus formed varies from 14 to 24, the average being about 16. The complete cycle occupies 48 hours, but the process of active multiplication varies from 6-8. Completed schizogony coincides with the appearance of rigor in the malarial subject (Fig. 252, b, c). Different strains of this parasite are now recognized.

Gametogony.—When schizogony has proceeded for a certain period the young trophozoites become sexual forms (or gametocytes). In the immature stages they are difficult to distinguish from schizonts of a similar age, but soon they can be recognized as small, solid forms. Growth is much slower, the gametocyte taking nearly twice as long to mature as a schizont. No vacuole develops in the cytoplasm; it is less active, and hence fails to exhibit the manifold changes in form seen in the growing schizont. Pigment is produced in greater quantities, being more evenly distributed without clumping. The macrogametocyte (or female form) (Fig. 252, j) is much larger than the mature schizont, being 12-14 μ in diameter,

whilst the *microgametocyte* (or male form) is smaller (Fig. 252, i). Other distinguishing features in the *microgametocyte* are the large diffuse nucleus spreading across the body in the shape of a spindle, and the hyaline protoplasm, which stains a pinkish blue with Romanowski stain. The nucleus of the *macrogametocyte* is small, compact and stains more deeply; the cytoplasm is granular, non-vacuolated and stains intense blue. As a rule *macrogametocytes* are more numerous in the blood than are *microgametocytes*. Both appear in the blood in about six days, but do not mature for forty-eight hours; they probably also develop in the bone marrow. (Mosquitoes may be infected as early as the seventh day, but in artificially-produced blood infection it may be as early as the fourth day.)

The tissue cycle (or the E.E. cycle) of the malaria parasites has now been proved to take place in the hepatic cells (in *P. vivax*, *P. malariae*, *P. ovale* and *P. falciparum*). The primary protozoal mass in the liver is known as a *cryptoschizont*, which divides later into *cryptomerozoites*. There are thus four distinct cycles of development—the *pre-erythrocytic*, the *exo-erythrocytic* in the liver cells, the *erythrocytic* in the red blood corpuscles, and the *sexual* commencing with the growth of gametocytes in the blood and continuing with *sporogony* in the tissues of the mosquito. The *exo-erythrocytic* cycle of *P. vivax* is graphically illustrated in Fig. 260.

P. vivax is capable of maintaining itself (after a single infection) in the human body for a maximum period of about three years, but it usually dies out sooner. An exceptional period of nine years has been recorded by Garnham.

QUARTAN (*Plasmodium malariae*) (Pl. II C, facing p. 70)

This parasite has a localized and patchy geographical distribution. Its chief characteristics are the mildness of the febrile attacks which it occasions and its ability to produce relapses over a long period. The parasite is more solid than other species and produces quantities of dark pigment. It is, therefore, the *pigmented parasite*. It is usually scanty in the peripheral blood, and attacks predominantly the ageing erythrocytes which are about to be removed from the

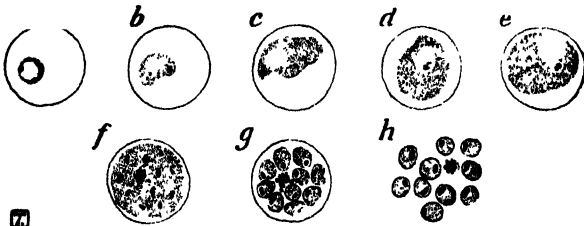


Fig. 253.—Quartan parasite, asexual cycle : stained.

circulation and thus provides a limit to parasitæmia. Quartan has a cycle in the peripheral blood of 72 hours. The ring, or young trophozoite, usually has a signet-ring appearance, and resembles that of *P. vivax*, but is usually more solid. Amoeboid movement is feeble, so that the irregularly shaped forms frequently seen in benign tertian are not found in quartan infections. Later still, when fully pigmented, amoeboid movement ceases (Fig. 253, d). The parasite then has a sharp outline and frequently grows across the corpuscle, producing a ribbon or band-shaped appearance. The nucleus is large and tends to be elongated. The pigment is usually deposited at the periphery of the parasite.

The host cell is not enlarged, but may contract and become somewhat smaller. Schüffner's dots are not produced, but stippling (Ziemann, or James' stippling),

consisting of small and less distinct fine dots and points, can be revealed by special alkaline Romanowsky staining for 30 minutes. The pigment is dark brown and coarse, and the oscillation of individual granules less marked than in *P. vivax*.

Schizogony.—The fully developed schizont (Fig. 253, *f, g*) is distinctly smaller than the corresponding phase of *P. vivax*, rarely exceeding 6.5μ , and the parasite does not occupy the whole red cell. Nuclear division commences after the schizont has been growing for 48 hours and proceeds slowly. The number of merozoites is small, from 6 to 12, symmetrical in arrangement, producing a daisy-head appearance. The individual merozoites are larger than in *P. vivax* and average 1.75μ . These segmenting forms are more frequently seen in the peripheral blood than the corresponding phase of other parasites (Fig. 253, *h*).

Gametogony.—The growing gametocytes do not assume the band form of the growing schizont. The young *macrogametocyte* is heavily pigmented and contains a smaller quantity of chromatin than the schizont of the same size, but the *microgametocyte* has more chromatin, a band-shaped nucleus, faintly-staining protoplasm and completely fills the corpuscle. It is a curious point that gametocytes of both sexes are particularly scanty in the blood. On the whole, the microgametocyte is slightly smaller than the macrogametocyte. The quartan parasite lives longer in the peripheral blood than the benign tertian, and persists for six, or even as long as twenty-two years. According to Shute and Maryon this species is difficult to transmit by *Anopheles maculipennis atroparvus*, but *A. stephensi* is a much more efficient carrier, on the whole. *P. malariae* develops more slowly in mosquito's stomach than does *P. falciparum*. In Liberia, on the other hand, Muirhead-Thomson (1957) finds the development in *Anopheles gambiae* much more rapid. The oöcysts differ from those of other human species of *Plasmodium* (Fig. 264). Up to the sixth day the pigment is coarse and resembles that of *P. falciparum*, but after that date a marked clumping of the pigment is observed. The intrinsic incubation period in man of the quartan parasite is never less than 20 days (Shute); in most it is between 21–59. It would seem that the average is 30 days and therefore the tissue phase in the liver are longer than in *P. vivax* or in *P. falciparum*. The sporozoites are longer and broader than those of *P. vivax* and *P. falciparum* and contain more chromatin.

Pre-erythrocytic and exo-erythrocytic cycles.—The E.E., or tissue cycle of *P. malariae*, has been worked out by Bray (1960). Garnham worked with *P. inui*, a parasite of *Macaca irus* which resembles *P. malariae* very closely and is regarded as the analogue of that parasite in monkeys. Pre-erythrocytic schizogony is observed in the liver from the seventh to twelfth days. The earliest stage is 5.5μ in diameter with five nuclei: the most mature about 22μ with over 2,000 merozoites. The cryptoschizont is lobed, enlarges the host cell and the margin is vacuolated (Bray).

OVALE TERTIAN (*Plasmodium ovale*), Stephens, 1922

(Pl. II D, facing p. 70)

This species was discovered by Stephens in 1922 in a patient from East Africa, though previously described in 1914 by Ahmed Emin at Camaran (Red Sea). Yorke and Owen (1930) showed that the morphological features were maintained when the parasite was transmitted by direct blood inoculation, and later James and Shute succeeded in transmitting it through *Anopheles maculipennis*. It is, therefore, a distinct and constant species. It has a much wider distribution than was formerly thought, through Central, West and East Africa to Egypt and South Africa. It is especially common in Liberia (Bray, 1957), totalling 9 per cent. of the total parasite rate. Cases have been notified from Turkmenistan, Palestine, Philippines, Mauritius, Egypt, India, Venezuela and New Guinea.

P. ovale has several features in common both with *P. vivax* and *P. malariae*.

It produces, like the former, a tertian periodicity ; there is some enlargement of the host cell to $10\ \mu$, and Schüffner's dots are present. On the other hand, the parasite more nearly resembles *P. malariae*. It may best be described as a *quartan parasite in a benign tertian cell*, or a round parasite in an oval cell. The pigment is not so heavy as in quartan. The small rings have no special features, but lie in red blood corpuscles, which are usually oval with fimbriated margins (hence the specific name of the parasite). Early stippling of red blood corpuscles containing rings is a feature of this parasite. Half-grown forms are non-amœboid ; the pigment is granular and brownish-black. The amount of chromatin and the distribution of pigment in a lateral band recall the quartan but, unlike the latter, "band forms" are not so common. The mature schizonts do not quite fill the host cell. The maximum number of merozoites may be twelve ; usually it is eight, and they are enclosed in a decolourized degenerated corpuscle with many Schüffner's dots ; occasionally two parasites are seen within one cell. The chromatin of the merozoites is crescentic and may bear accessory dots. The clinical course of the infection in man is usually mild and the parasite tends to die out after several paroxysms. (The maximum is about seven.) For this reason it is not very effective in therapeutic malaria. The paroxysm of fever produced by this parasite takes place towards the evening or at night. Slight variations from this account have been shown in the Donaldson strain studied in America (1954).

P. ovale takes longer than benign tertian to develop in anopheles—15 as against 10 days. The character and arrangement of the dark pigment in the oöcyst in the stomach wall of the mosquito is distinctive (known as the X pattern) and the sporozoites in the salivary glands are distinctly smaller than those of other species of plasmodium (Fig. 258, 10). In the Editor's experience *P. ovale* may persist in the body for two years without manifesting itself, despite the fact that the patient may have been treated for other varieties of malaria. The tissue, or E.E. cycle of *P. ovale* has been described by Garnham and colleagues (1954) in the liver of a volunteer. On the ninth day the mature cyptoschizonts resemble those of *P. malariae* more than those of *P. vivax* and produce about 15,000 large cryptomerozoites.

SUBTERTIAN OR MALIGNANT. (*Plasmodium fulciparum*)
(Pl. II A, facing p. 70)

Synonym.—*Laverania malariae*.—A notable feature in the identification of this parasite is its much smaller size ; the rings average 1.25 to $1.5\ \mu$, about $\frac{1}{4}$ the size of the corpuscle. Older rings may be indistinguishable from those of other species in size, but early phases, owing to their minute size and the narrowness of the cytoplasm, may be difficult to see (Fig. 254, a). The rings are usually sharp and regular. The nucleus is often divided into two, which may serve to

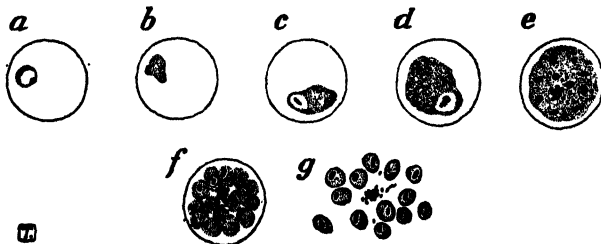


Fig. 254.—Evolution of the subtertian parasite : asexual cycle.

distinguish it from similar forms of the benign tertian. Multiple invasion of the corpuscle is often encountered and is very characteristic; it is doubtless due to the prodigious number of parasites present. Another characteristic of the young subtertian parasite is its tendency to apply itself to the margin or edge of the corpuscle—usually known as “*accolé*” rim, marginal or “*appliqué*” forms. They may appear as short streaks with red nuclear dots, giving them a bacilliform appearance (Pl. II, facing p. 70) and may be difficult to recognize. Clumping of red blood corpuscles is frequently observed in blood-films and is reminiscent of flocculation in blood grouping. The parasitized cells are surrounded by non-parasitized erythrocytes.

As development proceeds, the invaded corpuscles are filtered out by the capillaries and small arteries of the viscera and bone-marrow. They are specially

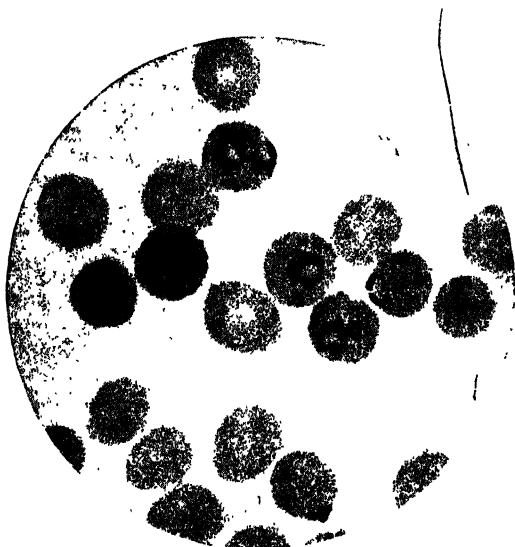


Fig. 255.—Trophozoites of *P. falciparum* showing Maurer's clefts, or spots, in erythrocytes. $\times 1,000$. (Microphotograph by Dr. J. Bell.)

numerous in the spleen and liver. In heavy infections, a few more mature forms may be seen; very occasionally a fully-segmenting schizont. On rare occasions all stages of schizogony may be observed in the peripheral blood, and in these prognosis is usually grave. The ring forms disappear before pigment is seen. As a rule, it is necessary to aspirate splenic blood, puncture the sternum or search the viscera (especially the liver or spleen) immediately after death, in order to demonstrate the more advanced stages of the parasite (Fig. 253, *c, d, e, f*). The whole cycle of schizogony is probably 36 to 48 hours. The size of the host cell remains unaltered. Schüffner's dots do not occur, but usually a few brick-red loops, streaks or dots, larger and more irregular in shape than Schüffner's are seen; these are known as “Maurer's clefts” or spots (Fig. 254). The loops are usually commoner with larger rings. In the fresh state the infected corpuscles have a slightly darker appearance, resembling old brass, hence they are often called “brassy bodies.” Pigment in the growing schizonts occurs in well-developed blocks, usually appearing as one dark conspicuous mass. Red blood corpuscles containing developing crescents contain a dark red rod which, if short, may be straight,

or, if too long for the cell, is twisted into a ring, loop or coil. These structures are best seen in deeply stained films.

Schizogony takes place within the capillaries of the internal organs. The fully-formed schizont measures $4.5-5\ \mu$ in diameter, so that it occupies only two-thirds of the red-cell. The number of merozoites (even with a single infection) varies from 8 to 32 (Fig. 253, g). The merozoites, much smaller than in other species, average 0.7 to $1\ \mu$. Schizogony does not proceed at a uniform rate and may vary from 36–48 hours. The forms in the internal organs are small and solid without vacuoles. The pigment is jet black and forms a single central mass, and on this account is apt to be mistaken for the quartan.

Gametogony.—The gametocytes assume the very striking crescentic shape (Fig. 257), but this description is not quite correct, for the ends are not pointed

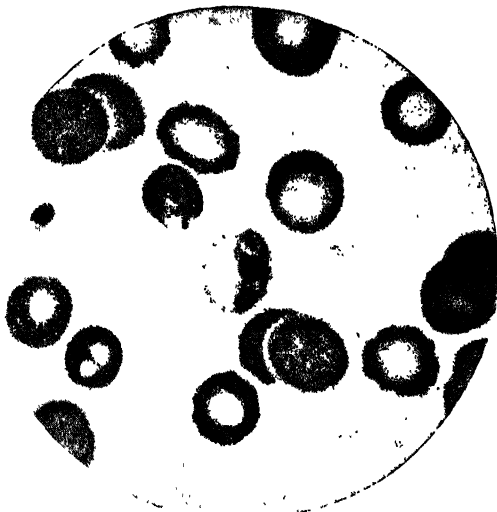


Fig. 256.—Formation of male gametocyte (crescent) of *P. falciparum*.
 $\times 1,000$. (Microphotograph by Dr. J. Bell.)

but more banana-shaped. (Fig. 256.) They are fairly large bodies, from 9 to $14\ \mu$ by $2-3\ \mu$ in breadth. A definite capsule appears to be secreted round the mature crescent (*gametocyte*). Crescents are not seen at the onset of the infection, but once they appear in the peripheral blood, they tend to increase in numbers during the next few days. They are less amenable to the action of quinine, chloroquine and atabrin than other stages of the parasite, and may persist in the blood for six weeks after subsidence of the fever; individual crescents have a life-span of 30–60 days. It has been noted that quinine administered at the commencement of a subtertian attack prevents the appearance of crescents. They are rapidly extirpated by plasmoquine (*pamaquin*) (p. 78) and paludrine, but are not affected by atabrin (*mepacrine*) or quinine. Two sexes of crescents can be distinguished. The *male* (*microgametocyte*) is broader and more stumpy than the female; the nucleus is diffuse and occupies the greater part of the protoplasm, and the pigment is scattered throughout the protoplasm and the cytoplasm is often pinkish blue when stained by Romanowsky stains (Fig. 257). The *female* (*macrogametocyte*) is more slender and possesses a small centrally placed nucleus with the

pigment concentrated round it. When the crescent is fully matured, the protoplasm of the corpuscle is completely engulfed, so that only the corpuscular envelope persists and may be distinguished as a phantom outline. Sometimes twin or double crescents have been seen in one corpuscle. It has often been remarked that in the most severe clinical types of subtertian malaria in Western and Central Africa crescents are few and in some instances cannot be found in blood-films, whereas in these same African infections, when examined later in England, they may be numerous.

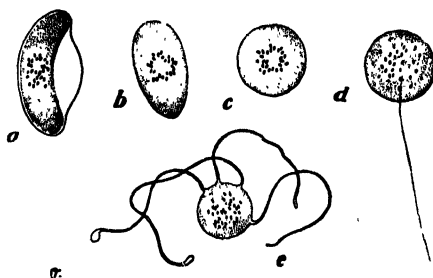


Fig. 257.—Evolution of the flagellated body from the crescent (male gametocyte).

(a) Male crescent (*microgametocyte*). (b, c, d) Changing into spherical form (*microgametocyte*).
(e) Eruption of flagella (*microgametes*).

In primary infections crescents appear in the peripheral blood with clocklike regularity on the tenth day after the onset of fever; by the fifteenth day have reached their maximum. If they have not appeared by the twelfth day they are unlikely to do so later. Female gametocytes can often be found two days before the males. Crescents are produced from specialized merozoites in the internal organs, but especially in the blood sinuses of the bone-marrow. The immature gametocytes are distinguished from schizonts of the same age by their elongated shape as well as by the scattered arrangement of the pigment. At first the nucleus is small, and is placed towards one end of the body, usually extending in a cross line one edge in the same way as the quartan. Subsequently the nucleus becomes centrally placed. In a large series of cases Shute and Maryon found that gametocytes developed in 55 per cent., especially those which recrudesced or relapsed after administration of sub-therapeutic doses of antimalarial drugs which appear to stimulate the production of sexual forms. The female gametocytes persist long after the male forms have disappeared. The gametocytes develop from asexual parasites present in the blood during remissions.

P. falciparum has a much shorter lifespan in the human body than other species. A single infection survives from one month to one year. Short term relapses may be very frequent, every two or three weeks over a period of one year or less, in the absence of adequate treatment. There are no long remissions or long term relapses as in *P. vivax*.

Strains of *P. falciparum* appear to differ greatly in virulence and in their susceptibility to antimalarial drugs, especially to quinine. According to Shute, some tropical strains cannot be transmitted through *Anopheles maculipennis* var. *atroparvus*, although this species is an efficient carrier of European strains of *P. falciparum*. Strains of *P. falciparum* develop readily in indigenous *Anopheles m. atroparvus* in the Roman Campagna, but Shute has proved that when these insects are taken to West Africa they prove refractory to infection in that area; but the same parasite develops readily in the laboratory in *Anopheles stephensi*, and a Roumanian strain does the same.

Morphological varieties of *P. falciparum* are thought to exist. A form with large rings is found in Africa and it has been claimed that blackwater fever does not occur with the small ringed form, but is associated solely with the former and is more often accompanied by Maurer's dots. Small hair-like rings are characteristic of a primary infection.

P. tenue, occasionally seen in India and Africa, has been regarded as a subspecies. This has large rings; "tailed" forms are seen in 10-12 hours, then there are "spider-web" stages, with tiny, spidery pseudopodia interlacing the corpuscle. Accolé forms are exceptional. That this is a variety of *P. falciparum* is to be inferred from its association with typical crescents.

The *pre-erythrocytic cycle* of *P. falciparum* has been described by Shortt, Fairley, Covell, Shute and Garnham in a human volunteer subjected to liver biopsy. Numerous mosquitoes—*A. maculipennis atroparvus* and *A. quadrimaculatus*—were infected from a patient harbouring gametocytes of *P. falciparum*. They were fed on the volunteer for three days in succession in the course of which 770 bites were recorded. The results were assessed 140 hours after the initial feed, when it was expected that the tissue forms would be found at three stages of development separated by twenty-four hours. These were found in the parenchyma cells of the liver. In shape they are oval and lobose. The fourth day form measured about $31\ \mu$ by $26\ \mu$, the fifth day $50\ \mu$ by $36\ \mu$, the sixth $60\ \mu$ by $30\ \mu$. The number of nuclei is much greater than in the case of *P. vivax* and increases with age. The oldest (140 hours) were in process of segmentation and some of them were already releasing small merozoites ($0.7\ \mu$ across) into the sinusoids. In some an apparent membrane was present around the schizonts, but they did not provoke any cellular reaction. The pre-erythrocytic forms resemble those of *P. vivax* and *P. cynomolgi*, but the mature schizont is considerably larger, whilst the merozoites are smaller and more numerous. Schizogony proceeds more rapidly. This similarity indicates that these three species are closely related. The pre-erythrocytic development, with liberation of cryptomerozoites, may be completed in less than 135 hours after mosquito transmission.

Abnormal malaria parasites.—Frequently, in the tropics, in hyperendemic areas, mixed infections of two, more rarely three, species of parasites may be found in the same individual. The usual combination is that of the benign tertian with the subtertian. Immature forms of both parasites may be demonstrated in the same microscopic field, but more usually various developmental stages of the benign tertian are seen with subtertian crescents; still more infrequently the two different species have been recorded within the same cell. In Ceylon and Malaya combined infection of benign tertian and quartan are not uncommon. Ever since the time of Schaudinn, certain puzzling appearances, especially in benign tertian infections, have been noted which were thought by him to denote a process of parthenogenesis, but it was recognized (J. D. Thomson) that this mulberry-like mass really consisted of a segmenting schizont and a gametocyte confined within a single red blood-corpuscle. Combined infection of schizont plus male or female gametocyte, or even twin gametocytes, have frequently been recorded. Multiple infections with two, three or even five subtertian rings are commonly seen in heavy infections.

Cultivation of malaria parasites.—Cultivation *in vitro* of malaria parasites was first accomplished by Bass (1911) and has since been amply confirmed. Asexual multiplication has been observed in the three main species, and in subtertian four successive generations have been obtained, but frequent subinoculations are necessary. The medium is defibrinated blood containing dextrose.

Crescents have been produced in artificial cultures of *P. falciparum* after 10 days incubation (Sinton). Some interesting facts have been observed in the morphology of the cultivated parasites; for instance, the number of merozoites formed during schizogony is considerably greater than in the blood-stream under natural conditions, whilst the parasitized cells show a tendency to agglomerate, a feature which does not take place in benign tertian cultures. *H. gallinacea* has been grown in tissue-culture by F. Hawking (1944), and this method is applicable to other species, such as *P. lophurae*.

Sporozoites can be preserved in viable form in deep-freeze (under $-70^{\circ}\text{C}.$). They are pooled in plasma, serum or saline. The ampoules are stored in a cabinet containing solid CO_2 , whereby a constant deep-freeze temperature is maintained. They remain viable up to 375 days. This provides a practical method for preservation of the parasite outside the host.

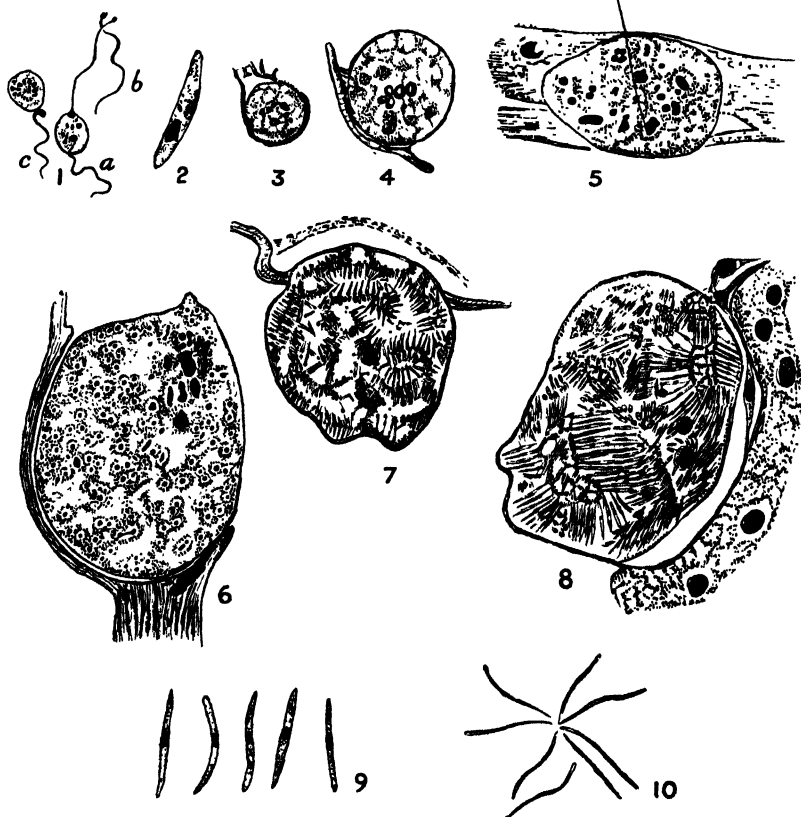


Fig. 258.—Stages in the development of *Plasmodium falciparum* in anopheles.
 $\times 2,000$. (After Wenyon.)

1. (a) Exflagellation of male gametocyte of *P. vivax*; (b) free flagellum (male gamete); (c) fertilization of female gamete. 2. Ookinete. 3. Encysted zygote in stomach wall. 4, 5, 6. Oöcysts showing reticulated cytoplasm. 7. Section of oöcyst showing sporozoites forming outgrowths from cytoplasmic reticulum. 8. Section of oöcyst into mature sporozoites. 9. Sporozoites from salivary gland. 10. Sporozoites of *Plasmodium ovale*. (After Shute.)

Sexual Forms.—The gametocytes of the four human species of malaria parasites differ in shape. In the *benign tertian*, *quartan* and *ovale* they are round or oval, but crescentic in the *subtertian*. The "crescent" exhibits no amoeboid movement and contains needle-shaped pigment particles in its centre. In the male (*microgametocyte*) the protoplasm is hyaline with loosely arranged pigment; in the female (*macrogametocyte*) the protoplasm is faintly granular with the pigment arranged in a well-defined ring. In the subtertian, gametocytes are derived from corresponding stages within the red corpuscles agglomerated in the blood vessels of the internal viscera. It has been proved that injection of blood containing gametocytes into non-immune individuals does not produce malarial infection.

The flagella, or *microgametes*, are formed of a chromatic filament and a covering of protoplasm, and after their eruption the remains of the parent cell consists of pigment granules and a small amount of residual protoplasm which are ingested by wandering phagocytes (mainly large mononuclears).

SUMMARY OF THE LIFE-CYCLE OF HUMAN MALARIA PARASITES (Fig. 259).

Malaria parasites belonging to the family Plasmodiidae undergo four cycles of development :

(I). The pre-erythrocytic development in the liver of the *sporozoite* derived from the salivary glands of the mosquito.

(II). The exo-erythrocytic cycle with the development of exo-erythrocytic (*cryptozoic*) schizogony which takes place in the liver cells in the case of the human species of Plasmodium.

(III). Asexual *erythrocytic cycle* by schizogony in the red blood corpuscles of the circulating blood.

(IV). The *sexual cycle* commencing with the growth of gametocytes in the vertebrate host and continuing with *sporogony* in the stomach cells of the mosquito.

As the descriptions of the full life-cycle of malarial parasites have necessitated an extension of the nomenclature, it is necessary to define some of the terms which are now coming into general use.

Prepatent period.—Following inoculation of sporozoites there is a short period of half an hour when the blood is infective if inoculated in large quantities. This phase is followed by a period during which no infected erythrocytes can be found and the blood is non-infective. This *prepatent period* is fairly constant in duration.

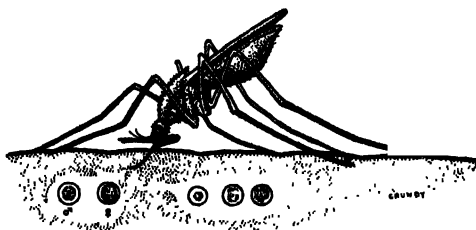
Pre-erythrocytic schizogony.—This term refers to the development of the sporozoite during the incubation period. It may occupy one generation only, as in mammalian malaria, or several generations, as in the avian forms.

Exo-erythrocytic schizogony.—It is necessary that this term should be confined to stages seen in the post-patent period—when the parasites have reached the blood and, in the case of the human parasite, have entered the liver cells.

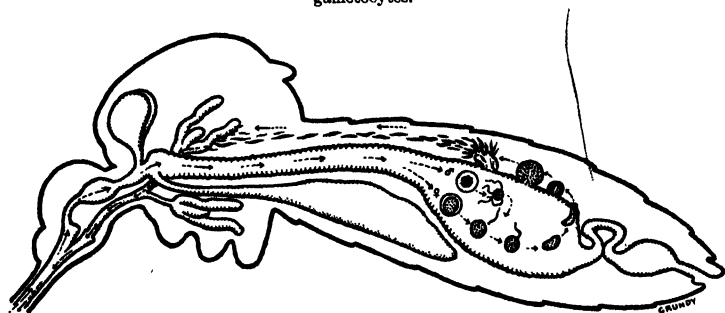
Tissue Phase.—As this term embraces both pre-erythrocytic and exo-erythrocytic schizogony, it should be used when the exact stage of the infection is unknown.

Phanerozoite.—Any exo-erythrocytic parasite except the pre-erythrocytic forms.

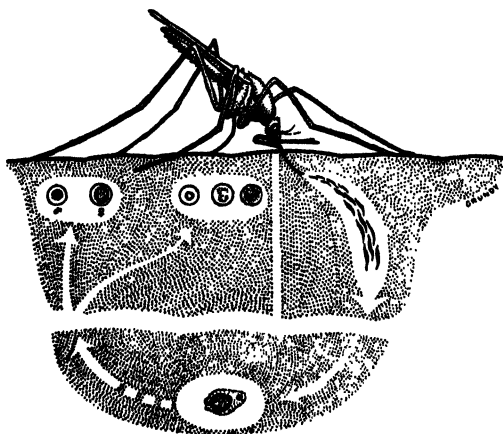
Cryptozoite.—This term has been introduced to denote the first stages in the development of the sporozoite. Cryptozoites are the product of the first division of the sporozoite and are contained in a cryptozoic schizont.



The female *Anopheles*, in feeding on a person with malaria, takes in blood containing the male and female gametocytes.



The male and female gametocytes fuse in the stomach of the mosquito, to become a single fertile egg-like body, which develops in the stomach wall, producing large numbers of sporozoites, which make their way to the salivary glands. This cycle lasts 7 days or more.



When, after the development of sporozoites, the infected mosquito feeds again on man, she discharge sporozoites into the human tissues; these may be detected in the blood for not more than $\frac{1}{2}$ hour after the mosquito has bitten. Thereafter they develop in the cells of the liver, and the malaria parasites to which they give rise may be found in the blood 7 to 9 days after the bite of the infected mosquito. The clinical attack of malaria usually begins within a day or two of their appearance in the blood. Exceptionally, in *P. vivax* infection, this process of development may be delayed for several weeks or months.

(Diagrammatic. The sizes of the parasites and mosquitoes are not in proportion to each other.)

Fig. 259.—The Malaria Cycle
(By permission of J. Hull Grundy)

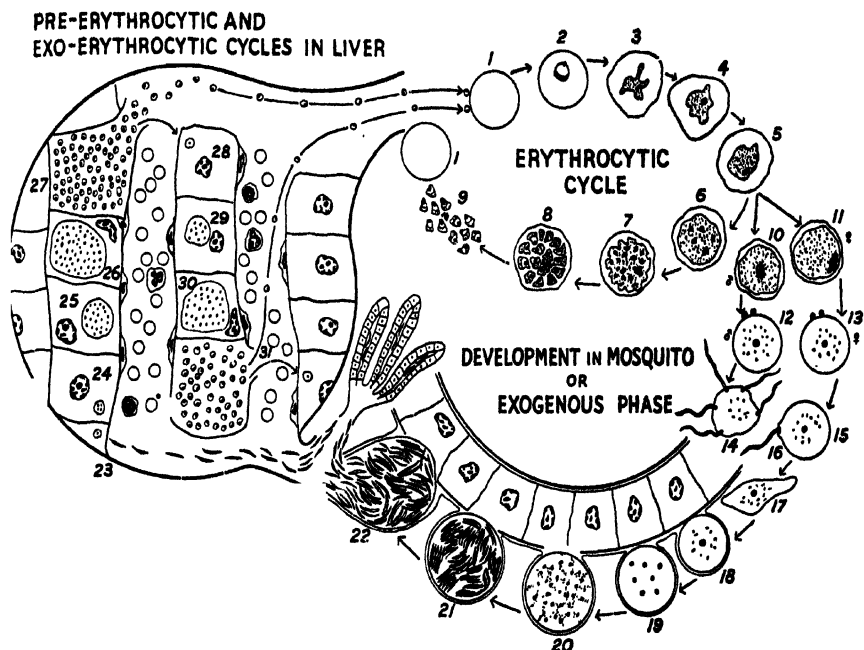


Fig. 260.—Schema of the complete life-cycle of mammalian malaria parasite based on *Plasmodium vivax* and *P. cynomolgi*. (After Shortt and Garnham.)

- 1, 1. Normal red cells.
- 2, 3, 4, 5. Red cells containing young parasites (trophozoites).
- 6, 7, 8. Erythrocytic schizogony.
9. Liberation of erythrocytic merozoites into blood.
- 10, 11. Development of male and female gametocytes in circulating blood.
12. Mature male gametocyte extruding polar bodies.
13. Mature female gametocyte extruding polar bodies.
14. Exflagellation of male gametocyte producing male gametes (microgametes) in stomach of mosquito.
15. Female gamete, or macrogamete, being fertilized by male gamete to become a zygote.
16. Male gamete or microgamete.
17. Oökinete, or travelling vermicule, formed by elongation of zygote about to penetrate epithelial lining of mosquito's stomach.
- 18, 19, 20, 21. Oöcysts developing on outer wall of mosquito's stomach.
22. Mature oöcysts rupturing and liberating sporozoites which enter salivary glands.
23. Sporozoite from salivary gland of mosquito entering liver cell of man.
- 24, 25, 26. Development of pre-erythrocytic schizont or cryptozoite in liver cells.
27. Pre-erythrocytic schizont liberating pre-erythrocytic merozoites (cryptomerozoites) which enter red cells, to commence the erythrocytic cycle, or to enter fresh liver cells to repeat the cryptozoic development, or exo-erythrocytic schizogony.
- 28, 29, 30. Stages of exo-erythrocytic schizogony ending in a second generation of merozoites (metacryptomerozoites).
31. Rupture of exo-erythrocytic cryptozoic schizont of any later generation to maintain cryptozoic cycle in liver, or to produce relapse by restarting the erythrocytic cycle by metacryptomerozoites.—(P.H.M.-B. and W. Cooper).

Metacryptozoite.—After the first cryptozoic generation there are schizonts which produce metacryptozoites, and the term includes all pre-erythrocytic stages with the exception of *cryptozoites*.

Micromerozoite.—Certain exo-erythrocytic schizonts consist of many nuclei



Fig. 261.—Pre-erythrocytic cycle of malaria parasites.

- 1.—Pre-erythrocytic (cryptozoic) schizont of *Plasmodium cynomolgi* in liver cell on 5th day.
- 2.—Pre-erythrocytic (cryptozoic) schizont of *P. vivax* on 7th day in liver cell showing form with two vacuoles.
- 3.—More advanced stage of pre-erythrocytic schizont of *P. vivax* showing formation and release of pre-erythrocytic merozoites (cryptomerozoites).

(After Shortt and Garnham, 1948, *Trans. Roy. Soc. Trop. Med. & Hyg.*)

and little cytoplasm and these microschizonts produce large numbers of micromerozoites. In size and structure, they resemble the merozoites resulting from schizogony in red blood corpuscles and are destined to enter them.

Macromerozoite.—These are larger bodies than the micromerozoites and they are fewer in number. They do not invade red blood corpuscles, but enter tissue cells.

Schizonts.—The term schizont is properly applied to an intracellular asexual form in any stage, but in practice it is restricted so as to designate asexual forms other than ring forms. When chromatin has fully divided with formation of merozoites, the schizont is known as an adult schizont, sporulation form, segmentation form, or rosette.

THE SEXUAL CYCLE IN ANOPHELES.—The sexual cells are male or female (*micro- and macrogametocytes*) in the blood of man and are incapable of further development, except in the appropriate mosquito. In the male the nucleus divides, the daughter-nuclei proceeding to the periphery become the nuclei of the fine filaments which are endowed with motile powers (*microgametes*). The female gametocyte (*macrogametocyte*) sheds *polar bodies*, becomes spherical (*macrogamete*) and is ready for fertilization by the *microgamete*. The impregnated macrogamete (or *zygote*) becomes mobile, elongates and as an *ookinete* bores its way through the lining epithelium of the mosquito's stomach, breaks up by *meiosis*, encysts between the epithelium and the limiting membrane and becomes an *oöcyst* (Fig. 260). The original nucleus of this cyst divides repeatedly,



Fig. 262.—Pre-erythrocytic schizont of *P. falciparum* in human liver, 6th day.
(After Shortt, Fairley, and others.)

the protoplasm segments around the daughter-nuclei forming a *spongioplasm*. Eventually these nuclei arrange themselves on the surface of the protoplasm in which the *sporozoites* (about $9\ \mu$ in length)¹ are formed, each nucleus acquiring an appropriate amount of cytoplasm. When fully filled with sporozoites the oöcyst bursts, setting them free. Some pass into the salivary glands of the mosquito (Fig. 263), then travelling *via* the salivary ducts they once more enter the blood when the mosquito proceeds to feed on its next victim, and are carried to the liver to recommence the pre-erythrocytic cycle. Not only are the sporozoites found in the salivary apparatus, but the whole body cavity becomes choked with them, and they may even penetrate the legs and antennæ.

The oöcyst also contains pigment granules, and one or more residual cytoplasmic bodies. The number of oöcysts present in the stomach of a single mosquito varies with the number of gametocytes in the blood. Sometimes only one or two oöcysts occur; sometimes ten to twenty; exceptionally there are large numbers.

The optimum conditions for development of malaria in anopheles are a mean temperature of 20–25° C. with a mean relative humidity of 60 per cent. or over.

¹The structure of the sporozoite, studied by Garnham, Bird and Baker by electron microscopy, is elaborate. The head is provided with an apical cup, peripheral fibrils, mitochondria and elongated, paired organelles.

At a constant temperature of 15° C. *P. vivax* ceases to develop, but *P. malariae* continues to grow at 16.5° C. At 20° C. the cycle in *P. vivax* occupies 16 days, in *P. falciparum* 22, and *P. malariae* 32–35.

Mosquitoes infected with *P. vivax* may be chilled; development of the parasites is merely temporarily arrested, but in *P. falciparum* the oöcysts shrivel if kept at freezing point for 48 hours. In some species of anopheles, although 50 or more oöcysts may be found in the stomach, full development does not proceed further. When once sporozoites have been developed the infected anopheles is capable of producing infection at extremely low temperatures and remains infective for three months.

In malaria man constitutes the *intermediate* (asexual cycle) and the mosquito the *definitive* host (sexual cycle).

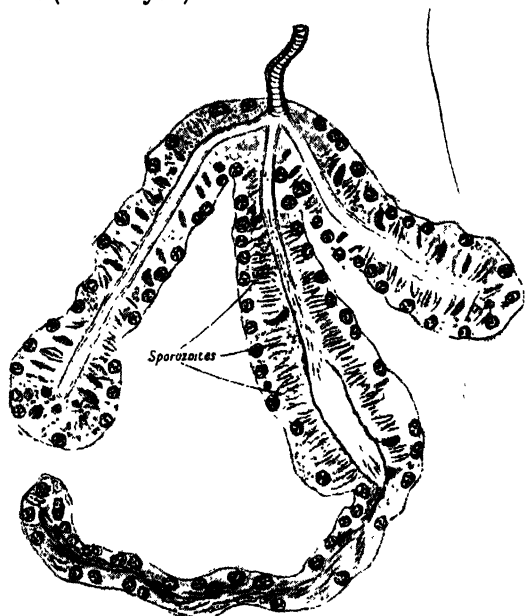


Fig. 263.—Salivary gland of *Anopheles maculipennis* containing sporozoites of *Plasmodium falciparum* compiled from serial sections. (After Wenyon.)

Differential characters of the oöcysts of various species of malaria parasites.—According to Shute the oöcysts of the four species of human plasmodium exhibit differentiating characters in the arrangement and number of the pigment granules. In *P. vivax* the pigment is scattered without any definite pattern; the granules are fine, yellowish-brown and exceed 70 in number. In *P. ovale* the pigment forms a definite pattern. It is coarser and darker in colour than in *P. vivax*, less so than in *P. falciparum* and *P. malariae*. The number of granules in an oöcyst seldom exceeds 50. In *P. falciparum* the pigment forms a definite pattern, is jet black and very coarse. The number of granules in an oöcyst rarely exceeds 20. In *P. malariae* they are also coarse and dark and the number of pigment granules less than 20 (Fig. 264).

Recognition of oöcysts and sporozoites by dissection.—No particular difficulty should be encountered in recognizing malarial oöcysts, even under a

low power of the microscope. They are spherical, refractile bodies which jut out beyond the stomach cells. With a higher power ($\frac{1}{4}$ in. lens) characteristic black pigment can be discerned in their interior.

There are some misleading appearances, such as large body-cells ("pancreatic cells") and other objects, such as gregarine cysts and larval nematodes, which may occur in the anopheline stomach. Sporozoites may be recognized as fine refractile bodies in the cells of the salivary glands (Fig. 263). The sporozoite rate is the percentage of anopheles caught in nature which, when dissected, show sporozoites in the salivary glands.

Ross's black spores.—Sometimes oöcysts may be encountered in which the cyst wall is completely filled with dark brown or black masses, which appear to represent degenerated cell contents which have undergone chitinization comparable to chitinized larval filariæ (Fig. 194, p. 730). Mayne claimed that these black spores are always associated with branches of the tracheal system of the mosquito. There is, however, no general agreement of their nature. Some regard them as representing an invasion by a fungus, *Nosema*, which preys upon the oöcysts, but they are never encountered save in infected mosquitoes.

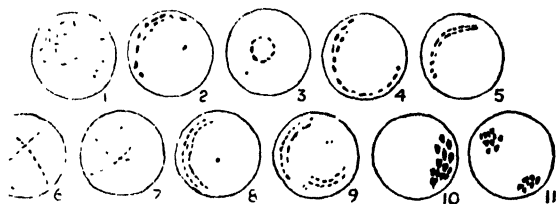


Fig. 264.—Diagrams representing typical arrangement of pigment granules in 3-4 day oöcysts. (After Shute.)

1, Benign tertian with golden-brown pigment. 2-5, Subtertian with black pigment. 6-9, Ovale tertian with dark brown pigment. 10-11, Quartan with coarse black pigment.

Infectivity of anopheles.—In endemic areas it is seldom that more than 4 per cent. of susceptible anopheles are found infected. (Christophers for *A. culicifacies*.) But when susceptible anopheles, such as *A. culicifacies*, *gambiae* and *maculipennis* (*elutus*, *labranchiae* and *atroparvus*) are fed on carriers rich in gametocytes, 90 or even 100 per cent. may become infected. Many factors in nature affect the infectivity of anophelines: e.g., the season, the number of infected malaria cases with gametocytes in their blood, and whether the insects favour human habitations or cattle sheds. In West and Central Africa 10 per cent. of *A. gambiae* and *A. funestus* are infected in nature. Shute and Maryon (1956) state that, when biological differences are present, they are exhibited by strains originating from distinct geographical areas, but not from the same locality. *P. vivax* from Madagascar, Roumania and French Cameroons vary in length of incubation period and in power of infectivity of different anopheles. The Madagascar strain acquired immunity against its own homologous strain and the number of oöcysts developing in the stomach of *A.m. atroparvus* varies also. *P. falciparum* from N. and E. Africa, Belgian Congo, Italy and Roumania varies in susceptibility to quinine and infectivity for *A.m. atroparvus*. Jeffery and Eyles (1955) found that infectivity of mosquitoes to *P. falciparum* is related to the density and duration of infection. Mosquitoes frequently became infected when fed on gametocyte densities of less than 10 per cmm. of blood and were infected so late as 231 days of parasite patency in S. Carolina and 410 days in the Panamanian strains.

Shute has found that 100 per cent. of *A. maculipennis atroparvus* become infected with *P. vivax* when fed on carriers with gametocytes exceeding 4,000 per c.mm., but with *P. falciparum* rarely more than 50 per cent. become infected with a single feed. This has been confirmed by Boyd in Florida with *A. quadrimaculatus* and by Green in Malaya with *A. maculatus*.

In Bombay Bentley showed that 18 per cent. of *A. stephensi* were naturally infected in August, but none in the dry season. Similar variations in the infection rate have been found in Holland in *A. maculipennis* (Swellengrebel). In America the infection rate of *A. quadrimaculatus* is 0.57 per cent., but in negro habitations it was as high as 4.9 per cent. (King). The fact that any particular species of anopheles can be infected in the laboratory does not by any means

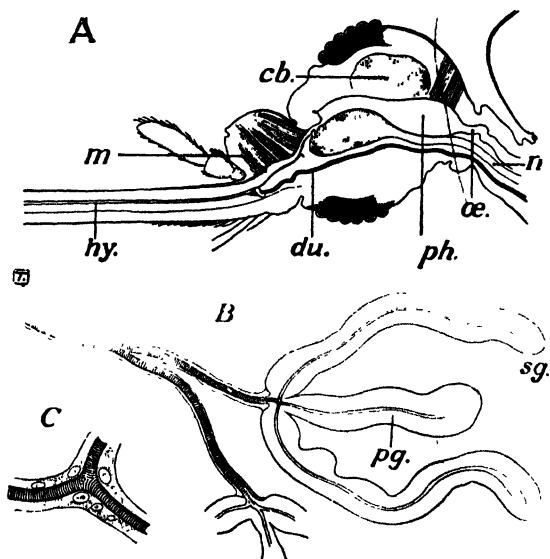


Fig. 265.—Dissection of head of mosquito.

A, Median section of head, showing *du.*, the veneno-salivary duct, with its insertion in *hy.*, the hypopharynx; *cb.*, cerebrum; below this are the cerebellum and the pumping enlargement of *æ.*, the oesophagus; *m.*, muscle; *n.*, nerve-commissure. The other parts have been removed. B, The veneno-salivary duct, showing its bifurcation and the three glands on one of its branches; *pg.*, poison gland; *sg.*, marks the upper of the two salivary glands. C, The bifurcation of the duct with its nucleated hypodermis.

prove that it is capable of transmitting malaria under natural conditions, because this is a question of bionomics. Thus in Holland, England and Italy *A. maculipennis* vars *messeæ* and *typicus* play no part in malaria transmission, because they are *zoophilic*; they are easily infected in the laboratory, when they can be induced to bite man, and in North Roumania and Bessarabia they are important carriers, domestic animals being scarce there. In England, however, *A. m. typicus* has not been found, only *atroparvus* and *messeæ*.

COCCIDIOSIS

SUBCLASS: COCCIDIA. ORDER: EIMERIIDEA

Coccidia are intracellular protozoa with a life-cycle consisting of alternation of generations—an asexual cycle (*schizogony*), alternating with a sexual cycle (*sporogony*). A single zygote encysted as an *oöcyst* produces secondary cysts or

sporocysts, which give rise to a number of sporozoites. The life history of a typical coccidium (*Eimeria*), which causes disease of the rabbit liver, closely resembles that of the malaria parasite. This fact led Pfeiffer in 1892 to predict, with some accuracy, the probable cycle within the mosquito. The sporozoites, liberated from the sporocyst, penetrate epithelial cells where they develop into schizonts, characterized by a vesicular nucleus and karyosome. The nucleus divides by repeated fission till a number of daughter-nuclei are produced and the schizont divides into as many merozoites. When the cell bursts, *merozoites* are set free and, entering other cells, develop either into *schizonts* or *gametocytes*, both male and female.

The male gametocyte develops by mitosis of the nucleus, forming *microgametes*, which are small, slender bodies. When the host cell bursts, these microgametes are liberated and enter the female cell (*macrogamete*). The fertilized cell (*zygote*) secretes a tough membrane and becomes an *oöcyst*.

The nucleus of the penetrating microgamete then fuses with the female nucleus (*synkarion*). The zygote breaks up into four *sporoblasts*, which, when enclosed by a tough envelope, are known as *sporocysts*, and within this the protoplasm divides into two *sporozoites*. In order to develop further, the oöcyst has to pass out in the faeces and be swallowed by a new host, whereupon the tough membranes dissolve and *sporozoites* are liberated.

Eimeria stiedæ is a common parasite of the rabbit. A somewhat similar coccidium has been reported in the human liver, and named *E. gubleri* (Guiart, 1922). The first cases of hepatic coccidiosis in man was described by Gubler in 1858 and by Virchow in 1860; three more were reported by Dobell in 1919. Luis Léon, of Quito, Ecuador, found an authentic case there in 1959 in which the

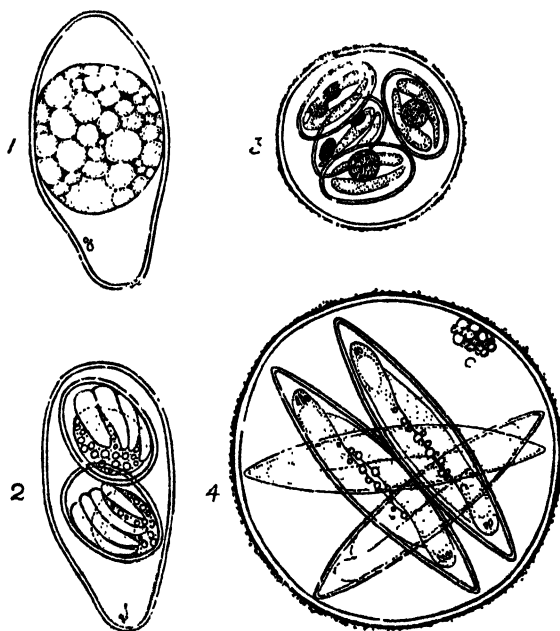


Fig. 266.—Oöcysts of coccidia found in human faeces. $\times 1,000$. (After Dobell.)

1, *Isospora hominis*, undeveloped cyst. 2, Fully developed spores of same. 3, *Eimeria clupearum*, fully developed oöcyst and spores. 4, *Eimeria sardinia*, fully developed oöcyst and spores.

cysts were present in large numbers in the liver. (*Revista. Med. Mex.*, 1959.) This parasite has a special affinity for hepatic tissue. The cysts are ellipsoid, measuring $46\ \mu$ by $34\ \mu$. Woodcock and Wenyon originally discovered coccidial cysts (*Isospora*) in human faeces in 1915. Dobell (1919) described cysts of the genus *Eimeria* as occasionally occurring in man.

INTESTINAL COCCIDIOSIS: Genus *Isospora* *Isospora hominis* (Railliet and Lucet, 1901).

(Fig. 266, 1 & 2)

Synonym.—*I. belli*. (All authorities are not agreed that this synonym is correct. Hoare considers that *I. hominis* and *I. belli* are distinct; the former probably a parasite of the dog, the latter of man). The oöcysts are found in the faeces and have been seen in fluid from duodenal intubation (Elsdon-Dew, 1953).

Though undoubtedly a parasite of the epithelium of the small intestine, possibly the duodenum, this coccidium is not seriously pathogenic, though it may be the cause of a debilitating diarrhoea, in which the stools contain pus cells and Charcot-Leyden crystals, as shown by Connal in a technician who swallowed material containing ripe oöcysts of *I. belli*. In addition there are cysts in the faeces and associated eosinophilia, as in the cases described by Connal and the Editor. Nevertheless, the schizogonic cycle of development in the intestine is not yet known. The oöcysts are elongated, with tapering extremities; they vary in length from $18\text{--}33\ \mu$ and in breadth from $12\text{--}16\ \mu$. The oöcyst wall is clear and colourless; the contained *zygote* is usually unsegmented, but occasionally segmentation into sporoblasts has been observed. Further development takes place in the faeces: two ovoid sporoblasts become enclosed in sporocysts measuring $14\ \mu$ by $7\text{--}9\ \mu$. In each eventually four sporozoites are produced.

Elsdon-Dew and Freedman (1953) recognize that there are at least two species infect man—one corresponding to *I. belli* (Wenyon) and the other to *I. hominis* (Railliet and Lucet) as follows:—

I. belli may be passed at all stages of development, immature forms mature in up to 5 days. Oöcyst $30\ \mu \times 12\ \mu$: sporocyst $11\ \mu \times 9\ \mu$. Usually no oöcystic residual body; sporocystic residual body finely granular with limiting membrane, compact and centrally placed between four sporozoites. The sporocysts are relatively larger than those of *I. hominis*.

I. hominis is usually passed fully developed. Oöcyst ball is usually absent. Sporocysts may be single or coupled in pairs, each being $15\ \mu \times 10\ \mu$. Sporocystic residual body of coarse loosely aggregated granules appearing polar in position, separate from the four sporozoites.

A single case of infection with *I. rivolta* (Grassi, 1879) has been reported and there is a possibility that *I. hominis* and *I. bigemina* (Stiles, 1891) are of the same species.

I. natalensis. This species, described by Elsdon-Dew (1954) resembles *T. rivolta* in its cystic stage. The cyst measures $30 \times 24 \times 21\ \mu$ and the sporocysts occupy an equatorial position and measure $17 \times 12\ \mu$. They contain an irregular residue of loose, coarse granules.

Isospora infections are specially common in Natal, and 78 cases were diagnosed within 9 months in 1958 (Walker and Bersohn).

Cysts of the genus *Eimeria* have been seen in faeces, but they are not really parasitic in man, but are passed through the intestine after eating fish infected with *E. clupearum* or *E. sardinae*. (Fig. 266.)

CLASS : ZOOMASTIGOPHORA
ORDER: PROTOMASTIGIDA :
FAMILY TRYPANOSOMATIDÆ
GENUS: TRYPANOSOMA
TRYPANOSOMES

The structure of trypanosomes is uniform in type, though subject to variation in minor details. The body is slender, tapering to a fine point anteriorly, whilst the posterior may be pointed or blunt. In general shape it resembles a curved, flattened blade. The terms "flagellar" and "aflagellar" are sometimes used to designate the extremities in place of "anterior" and "posterior," which are employed strictly with reference to the mode of progression.

The *nucleus* is centrally situated; the *kinetoplast* is usually placed posterior to the nucleus, sometimes in close proximity. The *axoneme*, the axial filament of the flagellum, arises from a *blepharoplast* and passes forward along the margin of the undulating membrane; in some cases it may terminate with it at the anterior extremity, but more usually it is continued forward as the flagellum (Fig. 267). Those trypanosomes, in which the axoneme extends beyond the anterior end, are said to possess a *free flagellum*. Multiplication usually takes place by binary fission. The blepharoplast and kinetoplast divide first; this is followed by

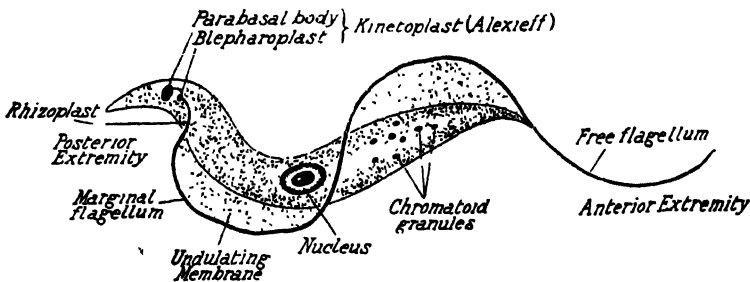


Fig. 267.—Schema of *Trypanosoma*. (After Dobell.)

mitosis of the nucleus and formation of a new flagellum and membrane. The body then divides longitudinally in an antero-posterior direction. Trypanosomes occur as blood parasites in all vertebrates, so that many wild animals harbour them and different species are specific to particular hosts and, in the majority of cases, appear to be non-pathogenic.

In this genus a convenient means of classification is afforded by the character of the flagellum: (1) If all the individual trypanosoma possess a free flagellum the species is monomorphic—e.g., *T. cruzi*. (2) If none of the individuals possesses a free flagellum the species is again monomorphic. There are no examples in man. (3) If some individuals of the species do, while others do not, possess a free flagellum, the species is polymorphic, e.g., *T. gambiense*.

Transmission.—With the exception of *T. equiperdum*, which passes from horse to horse during coitus, trypanosomes are transmitted by blood-sucking invertebrates, usually insects, but in fish and turtle by leeches. In *T. evansi* this transmission is mechanical and the blood-sucking fly, after feeding, within a short interval bites an uninfected host, in this manner inoculating directly those trypanosomes which adhere to the proboscis. In most cases, however, transmission is effected by a development cycle (cyclical development) in the fly, so that after an infective feed a definite intrinsic period is passed

through before the fly is capable of conveying the disease. The infective stage is then known as a *metacyclic trypanosome*. Two main types of development are recognized:

(a) *Anterior station*.—Development commences in the stomach of the fly, spreading forward to the proboscis and salivary glands, or it may be solely confined to the proboscis.

(b) *Posterior station*.—Development commences in the stomach and passes backwards to the hindgut.

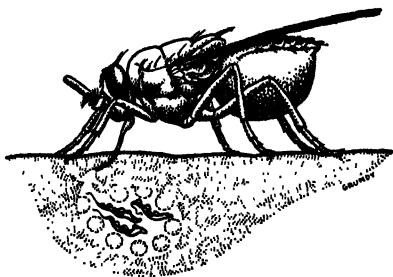
In the *anterior station* metacyclic trypanosomes are inoculated during the act of biting, whilst in the *posterior station* they escape in the faeces of the insect and infect their host through the mucous membranes, as in *T. cruzi*.

Pathogenic trypanosomes of Africa are transmitted by species of the tsetse fly, *Glossina*, in which three types of development in the anterior station are known to occur. In the case of *T. gambiense* (*Glossina palpalis*, *G. tachinoides*), *T. rhodesiense* (*G. morsitans* and *G. swynnertoni*) and *T. brucei* (*G. morsitans*), the ingested trypanosomes start to develop in the stomach, where long slender individuals are evolved, which in turn migrate forwards to the proventriculus, proboscis and salivary glands. There they are transformed into crithidial forms, which attach themselves to the gland cells and finally become metacyclic trypanosomes resembling the short stumpy forms normally found in the blood. These are inoculated with the saliva during biting. The whole cycle normally occupies a period of about twenty days. In *T. congolense* there is a stomach development, but long slender trypanosomes pass forward to the proboscis—not to the salivary glands, where crithidial and metacyclic trypanosomes are formed. In *T. vivax* there is no stomach phase, but trypanosomes develop within the proboscis through the crithidial and metacyclic phases.

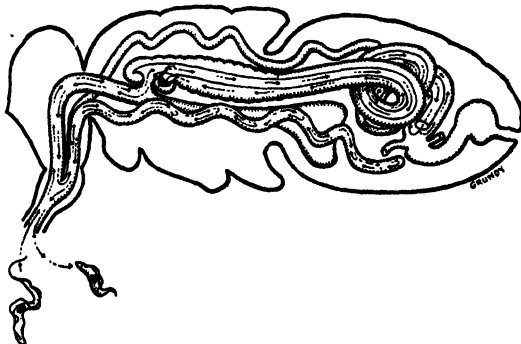
The *posterior station* method of development is exemplified by *T. cruzi* which is transmitted by reduviid bugs (*Panstrongylus*, *Triatoma*); development commences in the stomach and proceeds in the hindgut, where crithidial forms are produced and metacyclic forms escape from the intestine in the faeces.

In trypanosomes transmitted by the tsetse flies (*Glossina*) an important function is subserved by the *peritrophic membrane*, first elucidated by Hoare in the case of *T. grayi*. This is a soft cylindrical membrane extending from the proventriculus to the hindgut, where it is patent and is in reality a cylindrical tube suspended in the intestine. It is derived from an annular ridge or ring of gland cells in the proventriculus which secrete a viscous fluid which immediately solidifies as it is pushed progressively backwards. The ingested blood does not therefore come into contact with the gut wall, but osmosis takes place through the peritrophic membrane and the trypanosomes cannot penetrate it. Up to the fourth day the trypanosomes are actually within the lumen of the peritrophic membrane; they then migrate and escape through the open posterior end of this membrane and proceed to pass forward outside it to the proventriculus. They thus find themselves in a *cul de sac* and penetrate the membrane at the point of least resistance where it is still fluid. They then pass to the oesophagus and proboscis, to the end of the hypopharynx, and double back again to the salivary glands. There they become *crithidia*, attaching themselves to the salivary ducts for two to five days, before becoming *metacyclic* trypanosomes. The whole cycle occupies some twenty days. The fly is not infective until this stage is reached, but thereafter remains so for life (about eight months). Fairbairn (1958) has shown that in *T. rhodesiense* the trypanosomes migrate from the ectoperitrophic space of the midgut to the "anterior station" and that the trypanosomes can find their way through the membrane even at the front of the proventriculus (Fig. 268).

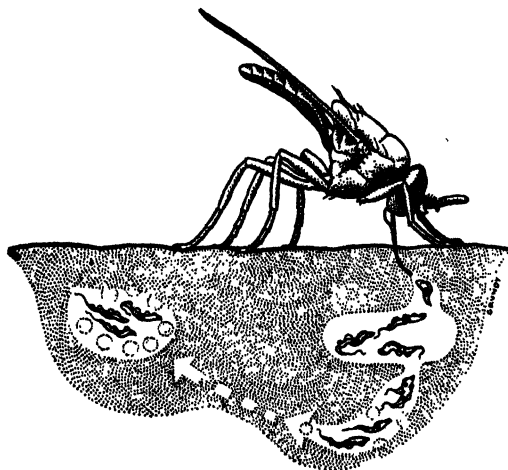
Infectivity of *T. gambiense* for *Glossina* is slight—less than 10 per cent. under experimental conditions; whilst in nature less than 1 per cent. are found infected.



The tsetse fly (male or female) takes up the blood of the sick person, which contains trypanosomes.



The trypanosomes enter the gut of the tsetse fly, and there they develop and increase in numbers by a process of division. The trypanosomes travel along the gut to the end of a lining membrane, and then they double back between it and the gut wall, passing into the proboscis and from there into the salivary glands.



From the salivary glands the trypanosomes are injected into animals (or man) at subsequent feeds. The whole cycle in the tsetse fly occupies about 20 days.

(Diagrammatic. The sizes of the parasites and tsetse flies are not in proportion to each other).

Fig. 268.—The Trypanosomiasis Cycle
(By permission of J. Hull Grundy).

Strains of *T. gambiense* vary in infectivity and this property appears to become lost in longstanding infections. In laboratory strains long absence from the natural vector is a factor. Polymorphism is also lost: only long slender forms may be encountered.

Mechanical transmission.—*T. gambiense* can survive in the proboscis of *Glossina* for varying periods and can be injected mechanically. Further, it has been shown in Nyasaland that *Musca spectandora*, feeding on exuded blood, can ingest trypanosomes and pass them out via the faeces into abrasions of the skin.

Cultivation.—Trypanosomes can be cultivated on certain blood-media: those of cold-blooded vertebrates and birds, as well as non-pathogenic species. *T. lewisi*, *T. theileri*, and *T. melophagium* are easily cultivated in N.N.N. medium or its modifications, but pathogenic species—*T. gambiense*, *T. rhodesiense*, *T. brucei*, *T. congolense*, and *T. vivax* cannot be maintained in these media, but grow in Razgha's medium, provided these strains have not lost their transmissibility by the tsetse. *T. cruzi* resembles the non-pathogenic species in its adaptability to artificial culture. As a general rule, in culture, trypanosomes tend to develop as in the invertebrate host, crithidial, and usually metacyclic, forms being produced.

Trypanosoma gambiense (Dutton, 1902) (Fig. 269, 1)

This trypanosome does not usually occur in the blood of man in any great numbers. Sometimes it is more readily revealed by gland or sternal puncture, or in the cerebro-spinal fluid. It varies greatly in length and breadth during different stages, as a general rule from 13–39 μ in length. The nucleus is central, the kinetoplast small and terminal, the undulating membrane well developed. Binary fission takes place in the blood, cerebro-spinal fluid, brain, kidney and, in the later stages, in serous fluids. Polymorphism in the blood is a characteristic feature. Three types are recognized: short stumpy forms without a free flagellum, long slender forms with free flagellum, and intermediate types. Posterior nucleated forms are now known to be developed in experimental infections in laboratory animals, as in *T. rhodesiense*, so that this feature is no longer recognized as peculiar to that species. The parasite occurs, not only in the blood, but in lymphatic glands, cerebro-spinal fluid, and the substance of solid organs, especially the brain. Most laboratory animals can be infected, but baboons (*Cynocephalus*) and the sooty mangabey monkey (*Cercocebus fuliginosus*) are refractory.

Reservoir hosts.—In the laboratory most African antelopes have been experimentally infected by the bite of the tsetse (*Glossina palpalis* and *G. tachinoides*), but under natural conditions this association probably does not hold good. The swamp-dwelling Speke's antelope, or situtunga (*Tragelaphus spekei*), is thought to be a reservoir and that *T. gambiense* can survive at least two years in its blood.

Speke's (*T. spekei*) is a handsome antelope, standing 36 in. at the withers. The buck possesses fine spiral horns. In ground colour it is uniform greyish-brown, and the head is adorned with white ocular and cheek spots with white chin. It is a very shy species, living in dense, impenetrable papyrus swamps, and so is seldom seen or shot by Europeans. The hoofs are long and widely splayed, but when it lives in dry land they become shortened and modified.

The rôle of native pigs in the Congo as a reservoir, though suspected, has not been established. *T. gambiense* is essentially a human trypanosome so that man himself forms the chief reservoir.

Trypanosoma rhodesiense (Stephens and Fantham, 1910) (Fig. 269, 2)

This is indistinguishable in human blood from *T. gambiense*, the same three types being recognizable. Until recently, it was thought that the production of posterior-nucleated forms in laboratory animals, especially the rat, was distinctive, but this is not so. In this host a change occurs in the nucleus, which assumes a position close to the kinetoplast or actually posterior to it. The proportion of posterior nucleated forms which are shorter than normal may be 50 per cent. in some laboratory animals. (Fig. 20, p. 120.) It has also been demonstrated that certain arsenical preparations, administered to animals infected with trypanosomes which have lost this trait, caused a reversion to type. Goats and horses infected with *T. rhodesiense* develop interstitial keratitis of the eyes, and the organism can be demonstrated in interstitial tissues outside the blood-vessels. Some authorities still regard *T. rhodesiense* as a human strain of *T. brucei*, with which it is morphologically identical. Others regard it as *T. gambiense*, of a more virulent



Fig. 269.—Various trypanosomes of man and animals. $\times 1,300$.
(After Wenyon.)

1, *T. gambiense*; 2, *T. rhodesiense* (*brucei*); 3, *T. evansi*; 4 and 5, *T. uniforme*, *T. vivax*; 6, *T. congolense*; 7, *T. cruzi*; 8, *T. theileri*; 9, *T. equinum*; 10, *T. equiperdum*; 11, *T. lewisi*.

race, transmitted by a different species of *Glossina*—*G. morsitans*—but this view has not gained much support. *T. rhodesiense* requires large quantities of glucose by the catabolism of which it obtains its energy. Under aerobic conditions pyruvate and, to a less extent, glycerol are the end products.

Geographical distribution.—*T. rhodesiense* is confined to North Nyasaland, North-East Rhodesia, Portuguese East Africa and Southern Sudan. Generally speaking its pathogenicity is greater than that of *T. gambiense*; it is more resistant to treatment and more virulent to laboratory animals.

Development in *Glossina* proceeds in *G. morsitans*, in the same manner as already described. In Tanganyika (Mwanza) it takes place in *G. swynnertoni*.

Reservoir hosts.—It is probable that a number of antelopes may harbour *T. rhodesiense* under natural conditions. Fairbairn and Burtt transmitted this trypanosome to humans by employing a strain which had been passed through various animals by *G. morsitans* for 10½ years.

R. B. Heisch, J. P. MacMahon and P. E. C. Manson-Bahr (1958) have now proved (for the first time) that the bushbuck (*Tragelaphus scriptus*) is the chief reservoir host, in Kenya, at any rate. This is a beautifully striped antelope which is widely distributed in Central and East Africa. It is a shy and wary species, closely allied to Speke's antelope (*T. spekei*) and which inhabits thick bush. The trypanosome, *T. rhodesiense*, was transmitted from this animal to two human volunteers, one European and the other African, and in whose blood this trypanosome was demonstrated. This infection was established by first inoculating rats with antelopes' blood and then transferring some of their trypanosome-infected blood to man, producing, at first, a "trypanosome chancre."

Trypanosoma cruzi (Chagas, 1909)

Synonyms.—*Schizotrypanum cruzi*; *T. escomeli*. (Fig. 269, 7.)

This trypanosome was first found by Chagas in the bug, *Panstrongylus*, and subsequently in man. It occurs in the blood of man in Brazil, Venezuela, North Argentina and in Central America (Panama, Guatemala) and is the cause of Chagas' disease. Trypanosomes, indistinguishable from *T. cruzi*, have been found by Malamos (1935) in the blood of *Macaca syrichta mordax* from Java, and again by Fulton and Harrison (1946) and by Seneca and Wolf (1955) in *M. mulatta* from India. This suggests the possibility that this disease has a much more extended distribution than hitherto supposed, but in the instances cited infection from accidental causes cannot be excluded. The first indigenous case recorded in the United States has been recorded by Woody (1955) in a child of nine months at Corpus Christi, S. Texas. At the same time naturally infected triatomid bugs have been found in California, Arizona and Texas.

In its life-history (Fig. 270) it differs materially from others by its manner of development. Some forms are broad, others narrow, but it invariably assumes a C-shaped attitude in the peripheral blood. Average individuals measure 20 μ in length. The posterior end is pointed and the kinetoplast is large. (Fig. 269, 7.)

Certain trypanosomes leave the bloodstream and invade muscles, especially the myocardium, or the cells of the brain or other organs, and there undergo a series of binary fissions during which they assume a leishmanial appearance. Multiplication is so rapid that soon large accumulations are formed in the tissues. Later, the leishmanial forms elongate and become crithidia; later still they become transformed into trypanosomes, which make their way through the tissues and enter the bloodstream.

Life history.—Trypanosomes are abstracted from human blood by a reduviid bug, *Panstrongylus* (*Triatoma*) *megistus*, in which they undergo a complicated development. This can take place either in larval, nymphal or adult stage of the insect. The trypanosomes pass into the midgut, become transformed into crithidia and as such continue to multiply rapidly. They enter the rectum, where metacyclic or infective trypanosomes appear and then pass out in the faeces of the bug. (Fig. 270, 1.) Inoculation of the parasite into man takes place by contamination of mucous membranes with faeces or by rubbing faecal matter into the wound originally made by the bug. Direct infection can take place on the lips and cheek (Garnham). Incidence of infection of bugs may be very high. In Brazil 41 per cent. of *P. megistus*; in Chile 50 per cent. of *Triatoma infestans* and *T. spinolai* and 37.5 per cent. of *T. protracta* infected in California. (Infection of monkeys with *T. cruzi* isolated from triatomid bugs in U.S.A. has been accomplished by Wood.)

These bugs live in cracks and holes in the thatch of primitive houses. Their bite is painless and usually occurs at the junction of mucous and cutaneous

surfaces as in the lip. Hence the name of "kissing bug." They bite at night, and retire to their hiding places before daylight.

Under experimental conditions, *T. cruzi* can be inoculated into rats, mice, rabbits, guinea-pigs and monkeys, and can pass through the mucous membrane of the mouth or conjunctiva. *T. cruzi* can be readily cultivated in liquid medium consisting of a solution of peptone, glucose and sodium chloride with coagulated

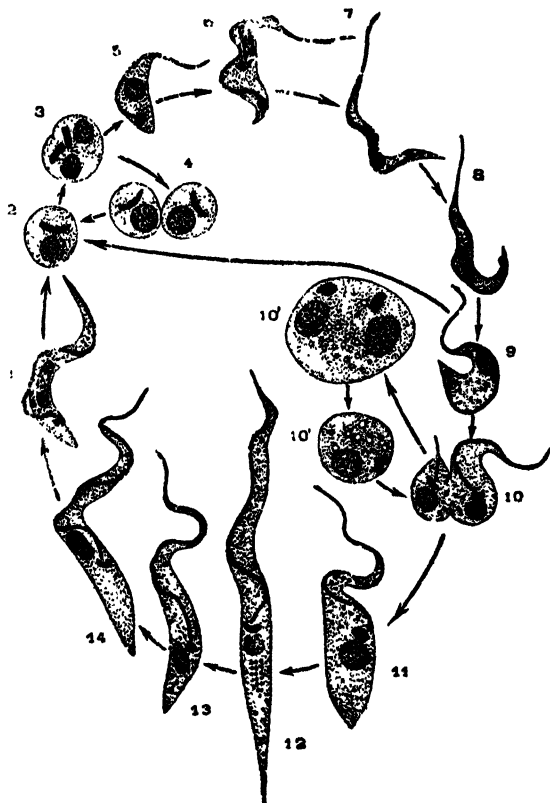


Fig. 270.—Evolutionary cycle of *Trypanosoma cruzi*: 2-9 in man or other vertebrate; 9-14 in *Panstrongylus*, *Triatoma* or *Cimex*. $\times 1,500$. (After Brumpt.)

- 1 Metacyclic trypanosomes infecting vertebrate; 2, 3, 4, schizogony in organs; 5-9, transformation of adult trypanosome (9); 10, crithidial form about to divide in small intestine; 10', leishmanian forms frequent in the proventriculus; 11-14, progressive transformation of crithidia forms into metacyclic trypanosomes (1) in hindgut.

rabbit blood corpuscles. Hawking (1947) has grown the parasite in tissue culture, using a suspension of trypanosomes from the blood of an infected mouse added to a culture of rat embryo. During the first two days great numbers of trypanosomes are present in the culture fluid, but after six days considerable numbers of intracellular parasites in all stages of development are seen in cardiac muscle, in macrophages and in the reticulo-endothelium.

A large number of reduviid bugs have been found capable of transmitting *T. cruzi*. In Mexico no less than fifteen species have been found naturally infected.

Amongst these are : *Triatoma phyllosoma*, *T. pallidipennis*, *T. rubida*, *T. barberi*, *T. dimidiata*, *T. picturata*, *T. longipennis*, *Rhodnius prolixus* and *Dypetalogaster maximus*. Other species in Brazil are *Panstrongylus megistus*, in N. Argentine, Chile, and Uruguay, *T. infestans*, *T. sordida*, *T. vitticeps*, *T. dimidiata* var. *maculipennis*; in Venezuela, *Rhodnius prolixus* and *Eratyrus cuspidatus*. Other species are *Eutriatoma maculata*, *E. nigromaculata*, *E. oswaldoi*, *E. patagonica*, *E. rubrovaria*, *E. sordida*, *Panstrongylus geniculatus*, *Psammolestes arthuri*, *P. coreodes*, *Rhodnius brumpti*, *R. domesticus*, *R. pullescens*, *R. pictipes*, *R. prolixus*, *Parabelminus carioca*, *Triatoma brasiliensis*, *T. carrioni*, *T. capitis*, *T. chagasi*, *T. cruzi*, *T. geniculata*, *T. hegneri*, *T. maculipennis*, *T. platensis*, *T. protracta*, *T. rubida*, *T. rosenbuschi*, *T. sanguisuga*, *T. spinolai*.

The incidence of infection with *T. cruzi* in some of the bugs may be higher; in Brazil 41.25 per cent. out of 2,412 *P. megistus*; in Chile 50 per cent. of *T. infestans* and of *T. spinolai*.

A species common in California (*Triatoma protracta*), extending as far north as Salt Lake City, harbours a trypanosome resembling *T. cruzi*, though the human disease is unknown there, whilst, under experimental conditions, other members of the *Triatoma* genus in the United States can be easily infected, as well as cosmopolitan species, *T. rubrofasciata* and *T. dimidiata* (Ecuador). In Arizona it is *Eutriatoma uhleri*; in New Mexico *E. protracta woodi*; and in Texas *T. gerstaeckeri*. It is probable that all species of *Panstrongylus* and *Triatoma* are susceptible to infection. Under laboratory conditions Brumpt has observed development in bugs, *Cimex hemiptera* (*rotundatus*), *C. lectularius*, *C. boueti*, *C. hirudinis*, and in ticks, *Ornithodoros moubata* and *O. savignyi*, but *O. hermsi* is resistant.

Reservoir hosts.—The multiplicity of the vicarious hosts of *T. cruzi* certainly indicates that the organism would spread to many countries, if other conditions remained favourable. These reduviid bugs are so easily infected that 100 per cent. become so at all stages of their existence and, moreover, remain so for the whole of their lives. The method of identifying *T. cruzi* in reduviid bugs is known as xenodiagnosis.

T. cruzi has been found in cats, dogs and pigs, but under wilder conditions it occurs mainly in several species of armadillo (Edentata), *Euphractus vellerosus*—the long-haired armadillo, *Dasypus novemcinctus*—the Peba armadillo, *D. novemcinctus fenestratus*, *Euphractus sexcinctus*—the six-banded armadillo, *Cabassous unicinctus*—the broad-banded armadillo, *Chetopractus vellerosus*, *C. pannosus*, *C. villosus carlinus*, *crassicauda*, and *paranalis*; in *Zoedypus pichiy*—the little armadillo, *Tolypeutes matacos*, and the tayra (*Tayra barbara*) in Brazil, all of which constitute the main reservoir hosts in country districts (Garnham).

Under experimental conditions all laboratory animals can be infected. Developmental forms of *T. cruzi* have been found in triatomid bugs as far north as Utah. In infected animals trans-uterine infection can take place and it has been claimed by Chagas that a similar process takes place in man.

Probably *T. cruzi* is naturally a parasite of armadillos, but occasionally becomes inoculated into man.

Other mammals include:

Canidae *Pseudolopex culpæus* (Colpeo Fox) *P. andinus*.

Pseudocyon gracilis.

Chiroptera *Histiotus cæphotis*, *H. montanus*, *Myotis nigricans*, *M. dinellii*, *M. levis*, *Carollia perspicillata*, *Antibeus jamaicensis*, *Desmodus rotundus marinus* (Panama), *Darius albiventer*, *Talirida macrotis*, *Glossophagosomina leachi*, *Carollia perspicillata azteca*, *Phyllostomus hastatus*, *Vroderma bilobatum* (Panama).

<i>Mustelidae</i>	<i>Grissonella huronax</i> , <i>G. rutellina</i> (Chilian Grisons), <i>Tayra barbara</i> (Tayra).
<i>Rodentia</i>	<i>Octagon degus</i> (Chilean bush rat), <i>Dasyprocta aguti</i> (Golden Agouti).
<i>Marsupialia</i>	<i>Didelphis azarae</i> , <i>D. paraguayensis</i> , <i>D. marsupialis mesoamericana</i> (California) (opossums), <i>Lutreolina crassicauda paranaensis</i> , <i>Marmosa cinerea</i> (Ashy opossum), <i>M. melachirus nudicaudatus</i> (Rat-tailed opossum).
<i>Anteaters.</i>	<i>Tamandua tetradactyli kriegi</i> .
<i>Sciuridae</i>	<i>Leptosciurus argentinus</i> —Argentine squirrel.
<i>Monkeys.</i>	<i>Saimiri sciureus</i> . "Saimiri."
<i>Rodents.</i>	<i>Neotoma fuscipes</i> —Woodrat (California). <i>N. albigula</i> (New Mexico, Arizona).

Backhouse and Bollinger have shown that the Australian phalanger or possum—*Trichosurus vulpecula*—is very susceptible.

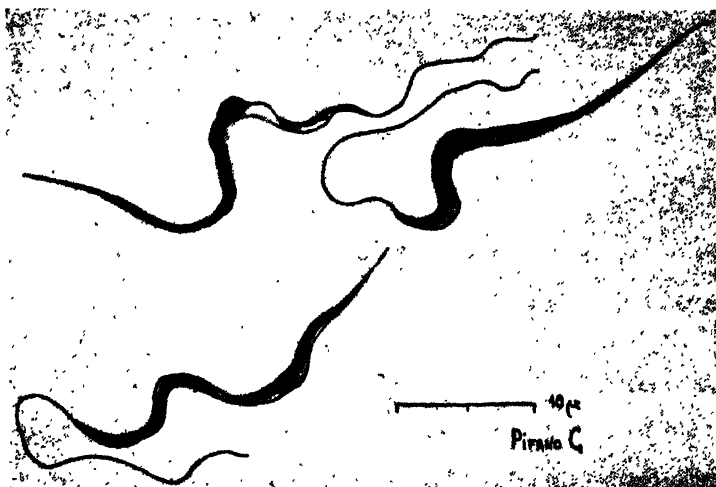


Fig. 271.—*Trypanosoma rangeli*. Forms in culture from the peripheral blood. (After Pifano and Mayer.)

Trypanosoma rangeli (Tejera, 1920) (*T. escomeli*, 1919)

This species occurs in Guatemala, Uruguay, Colombia and Venezuela.

It was first found in *Rhodnius prolixus* and subsequently sparingly in man, in the same districts where *T. cruzi* occurs. Human infections have been described by Medina, Pifano and Mayer, especially in children. According to Hernandez Paredes (1949) the illness in man is characterized by bouts of fever and sweats resembling exanthemic typhus. Pifano has recorded 41 human cases in Yaracuy (Venezuela) of which 31 had a double infection with *T. cruzi*. This trypanosome is readily cultured in citrated blood and glucose agar with defibrinated rabbit blood in Locke's solution. Positive inoculation in rabbits and white mice can be obtained.

The parasite is pear-shaped with a minute blepharoplast and much more elongated (50 μ) than *T. cruzi* (Fig. 271). Oval and crithidial forms are found in the intestinal contents of the bug and the latter forms in its faeces. The presence

of this parasite is best proved by xenodiagnosis and by blood culture on N.N.N. medium. Its pathogenicity is at present uncertain.

Trypanosoma ariarii. N. sp. Groot, Renjifo and Uribe (1950).—This is a long slender trypanosome, closely resembling *T. rangeli* and measuring 31 μ . Hoare and other authorities think it is identical. The body is markedly undulant, with two curves on one side and one to three on the other. Both extremities are thin and attenuated so that it is difficult to define where the anterior extremity of the body ends, and where the free flagellum begins. The posterior portion becomes progressively thinner and ends in a sharp, sometimes curved, point.

From 183 of the inhabitants examined by blood culture 67 showed these trypanosomes. One dog and a monkey—*Cebus fatuellus*—were found naturally infected.

Trypanosoma lewisi (Kent, 1879)

This is a common parasite of the rat and is present in considerable numbers in the bloodstream (Fig. 269, 11) at the height of the infection. It has once been recorded from man, in a Sikh child in Malaya (P. D. Johnson, 1933). The trypanosomes were present in large numbers in the peripheral blood for five days. It is, however, non-pathogenic to the rat. Individual trypanosomes vary considerably in size and appearance during the multiplication phase, but in the chronic stage average about 24 μ . The nucleus is situated at a point slightly anterior to the centre of the body.

T. lewisi develops in *Ceratophyllus fasciatus*, *Xenopsylla cheopis*, and other fleas. Trypanosomes enter the epithelial cells of the stomach, where they become spherical and grow. The nucleus divides repeatedly, and young trypanosomes are formed by multiple division. These pass into the hindgut, and after two days become crithidial forms. Eventually they escape as small metacyclic trypanosomes in the excreta. They are then ingested by the rat, which either licks up the flea faeces or devours the insect. Trypanosomes appear in the bloodstream after an incubation period of six days.

GENUS LEISHMANIA

The parasites of this genus are found in man in kala-azar, oriental sore and the South American disease—*espundia*. The leishmania of kala-azar is *L. donovani* in the Old World. In Brazil this parasite has been provisionally named *L. chagasi*, though its validity is doubtful. The organism of Mediterranean kala-azar, which is mainly confined to children, has been called *L. infantum*.

Cutaneous leishmaniasis in the Old World is caused by *L. tropica*, while the muco-cutaneous disease of South America is due to *L. brasiliensis*. Visceral leishmaniasis in dogs is attributed to *L. caninum*. All these parasites are morphologically identical and the claim that they can be differentiated by serological methods has not been substantiated. Possibly, differences in pathogenicity after artificial inoculation of susceptible animals, probably the hamster, may be forthcoming.

Under natural conditions, infection of animals with the human leishmania are exceptional, though cutaneous leishmaniasis has been found in gerbilles. *Pallasiomys erythrourus*, and *P. meridianus*. The animal reservoir of *L. donovani* in Kenya have been proved to be the gerbille (*Tatera vicina*) and the ground-squirrel (*Euzerus erythropus*) (R. B. Heisch and P. E. C. Manson-Bahr, 1958). In N.E. Persia in another species, *Rhombomys opimus*: In Middle Asia cats, dogs, Syrian bears and horses. The animal reservoirs listed in Brazil of *L. brasiliensis*, in Minas Geraes, are the Gibnut or Paca (*Cuniculus paca*), a large rodent, and the Pacarana (*Dinomys branicki*) or spotted cavy. In Honduras the "bay sore" and leishmaniasis of the ears (*Oreja de Chichleros*) is caused by *L. brasiliensis*. Garnham and Lewis (1958) have shown that it is probably a zoonosis, that the

reservoir is probably a small rodent, as in Panama it is the spiny rat (*Proechymys semispinosus*) and the vector is *Phlebotomus panamensis*. The Leishman-Donovan (L.D.) body is a small, round, oval, or cigar-shaped body from 1-3 or 4 μ in diameter. It consists of a minute mass of cytoplasm enclosed within a delicate membrane. Within is a nucleus and a kinetoplast. A rhizoplast is sometimes seen—a rod-shaped body representing the axoneme of the future flagellum, which is produced on artificial cultures and also within the gut of those sandflies (*Phlebotomus*) which serve as intermediary insect hosts for leishmania. In the visceral infection—kala-azar—the parasites (L.D. bodies) affect the reticulo-endothelium and are found, therefore, in endothelial cells, macrophages and plasmocytes, chiefly in the spleen, bone marrow and liver; in the skin, subdermal tissues and lymphatics in oriental sore (*L. tropica*), and in the skin and mucosa in espundia (*L. brasiliensis*). In zoological terms the L.D. body is classified as a leptomonad flagellate as is shown by its development in culture on artificial media.

Biological Species of Leishmania.—Adler (1957) after many years of investigation, thinks that enough evidence has been accumulated to show that the epidemiological aspects of leishmaniasis can be explained solely on the basis of biological species. By the application of serological methods the results become clear-cut. The biological species are the Mediterranean, Chinese, Indian, S. American, E. African and Sudanese, as well as, of course, *L. tropica* and *L. brasiliensis*.

The Mediterranean type produces uniform infection of the dermis in dogs so that usually 100 per cent. of sandflies become infected, depending, of course, upon the actual number of parasites in the skin. On the other hand, the infectivity of sandflies fed on humans is low. The leishmaniasis in dogs resembles that produced experimentally in the hamster. Therefore for the production of Mediterranean leishmaniasis in man the dog is essential. The South American is a unique type. It was not introduced from the Mediterranean, but is probably an autochthonous infection of the Brazilian raposa fox (*Lycalopex vetulus*). The Deanes (1954) found a high infection rate in these animals, transmitted by *Phlebotomus longipalpis*, but in this case sandflies are more easily infected direct from man than from the reservoir animal, in contradistinction to the Mediterranean form. As regards drugs the Indian and Chinese forms are amenable to antimony treatment, but it takes four times the necessary amount to cure Mediterranean kala-azar. In India, cultures of *L. donovani* will not infect man, but will infect animals. *L. tropica* in culture fails to infect animals, but will infect man, but, when injected into hamsters, it produces a generalized infection, but on reintroduction into man it gives rise to a local "oriental sore." Heisch has isolated *L. adleri* from a lizard which produces a quantity of antigen in common with the Kenya strain of *L. donovani*. *L. brasiliensis* has few antigens in common with *L. tropica*.

Method of culture.—The development of *Leishmania* in *Phlebotomus* follows upon the same general lines as that of insect flagellates of the genus *Leptomonas*. In the tissues of man, L.D. bodies multiply by binary fission and, as originally shown by Rogers, they develop in culture media into leptomonad forms resembling the flagellates of the dog-flea (*C. canis*.) (Fig. 272).

Fully developed leptomonad flagellates are 14-20 μ in length by 2 μ in breadth, and the flagellum measures 16-24 μ . They progress actively with the flagellum in front, and in cultures exhibit a tendency to agglomerate in clusters, or *rosettes*, with their flagella centrally directed.

The culture medium originally employed by Rogers consisted of spleen pulp added to slightly acidified citrate of soda solution, but N.N.N. medium is better. A small quantity of infected material from kala-azar, or blood from a vein, or

serum derived from the base of an oriental sore is added to the water of condensation in one or more of the tubes, which are then incubated at 22–25° C., and in 2–3 days flagellates appear in the fluid. It is essential that bacterial contamination should be excluded, and in this respect the addition of penicillin has proved to be of great advantage.

Life-history in the sandfly.—Ever since the finding of leptomonad flagellates in the sandfly (*Phlebotomus*) by Wenyon (1912) and the production of



Fig. 272.—Developmental forms of *Leishmania donovani* from the leishman body to the crithidial stage, and clumping of the flagellated organisms. $\times 2,000$. (After Wenyon.)

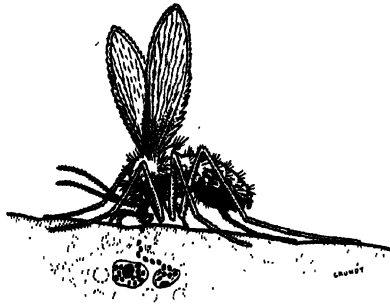
typical oriental sores by the inoculation of crushed-up *P. papatasi* by Sergent and his co-workers (1921), attention has been directed to the genus *Phlebotomus*.

The peculiar topographical distribution of kala-azar in India led Sinton (1922) to suggest that *Phlebotomus argentipes* might possibly be the insect intermediary. In more recent years intensive work by Christophers, Shortt, Knowles, Napier, Barraud, Lloyd and Smith clearly demonstrated that rapid development of leptomonad forms of *L. donovani* takes place in *P. argentipes* fed on the blood of kala-azar patients in India. The whole midgut becomes infected and the flagellates then pass to the pharynx and to the buccal cavity forming a block (Fig. 24, p. 136). The distribution of this species of *Phlebotomus* in India corresponds with that of kala-azar. In other endemic areas other species are involved: in China, *P. chinensis*, and *P. sergenti*, var. *mongolensis*; in the Sudan, *P. langeroni*, var. *orientalis*; in Brazil, *P. intermedius*; in the Mediterranean, *P. major* and *P. perniciosus*, and, possibly *P. perfliewi*.

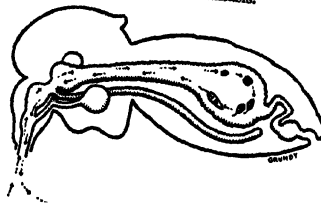
In India, *P. argentipes* readily infects itself by feeding on human cases when the organisms occur in sufficient numbers in the bloodstream. In the Mediterranean area the parasites are so scanty in the blood that the number of sandflies which become infected in this manner is negligible, though they commonly do so by feeding on dogs. Thus, in the Mediterranean, man is negligible as a reservoir compared with the dog. There is therefore a profound difference between the epidemiological character of Indian and Mediterranean kala-azar.

THE LEISHMANIASIS CYCLE

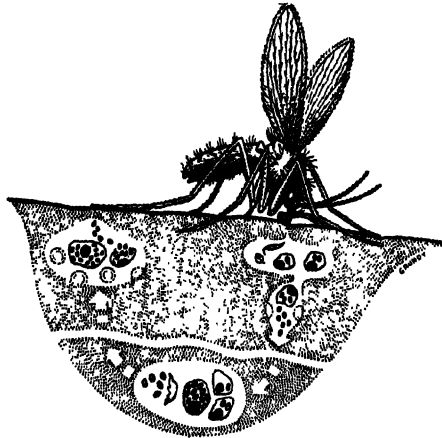
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The sand-fly takes up the leishmaniae (round forms), when it bites a patient (or dog) suffering from leishmaniasis.



The leishmaniae develop and increase in numbers by a process of division in the stomach of the sand-fly. They become elongated and move forward to the pharynx, and there multiply so greatly that they block the passage.



The sand-fly then injects the elongated, flagellate forms into man (or dogs) when it subsequently attempts to feed. The whole cycle in the sand-fly occupies about 10 days.
(Diagrammatic. The sizes of parasites and sand-flies are not in proportion to each other).

Fig. 273.—The Leishmaniasis Cycle
(By permission of J. Hull Grundy).

Difficulties were at first encountered by workers with sandflies, mainly on account of their delicacy and the difficulty of keeping them alive longer than five days after feeding. Then Shortt and his co-workers (1931) succeeded in transmitting *L. donovani* to hamsters (*Cricetulus griseus*) by the bite of infected *Phlebotomus argentipes*, but Swaminath, Shortt and Anderson (1942), by keeping these sandflies alive for two weeks after feeding on kala-azar blood, succeeded in conveying this disease to five out of an equal number of human volunteers. The sandflies were kept in an atmosphere of 28° C. and, after the original infecting feed on a kala-azar case, were fed on fruit juices in place of blood.

The cycle of development can be divided into two stages—after the first and second blood meals. First, the parasites enlarge and undergo binary fission; the flagellate leptomonads form on the second day; on the third they become elongated and active in the midgut, whilst short forms remain attached to the gut wall. On the fourth day they occur in masses near the proventriculus ("blocked" sandfly) and the fly is ready to lay eggs when ready for the second blood meal. Flagellates then move forward to the pharynx until they reach the proboscis. Transmission now takes place so that, when the sandfly next attempts to feed, the flagellates are dislodged from the buccal cavity and inoculated into the site of the bite (Fig. 273).

Susceptible animals. Dog.—In recent years conviction has been growing that the dog is the principal reservoir of the disease for man in the Mediterranean area. Adler stressed the importance of house as well as street dogs in Canea, Crete. In Marseilles, Giraud and Bergier showed that the majority of cases are derived from suburban residences where canine kala-azar is frequent. In Algeria Sergeant stated that the disease is transmitted by *Phlebotomus perniciosus* from dog to dog and from dog to man. Hoepli in China found that *P. chinensis* is readily infected from local dogs, and that this animal must be considered an important reservoir in that country. This was confirmed by Feng and Lee in Peking and by Andrews in Mukden (Manchuria).

Throughout the endemic centre of the Mediterranean area the disease is far commoner in dogs than in man; e.g. in Malta, out of a population of about 15,000 dogs, 10–12 per cent. are infected, whilst out of a population of 250,000 human beings about 90 cases occur annually. It is therefore not surprising that there are endemic centres, where dogs are infected in considerable numbers, and where there are relatively few human cases, as in Morocco and Marseilles.

In Brazil, Chagas and his colleagues, failing at first to find leishmaniasis in wild animals, succeeded in doing so in domestic dogs and cats, though it has now been found in caviés. In Malta, native dogs are found infected, especially during the summer. The majority are sick and emaciated. Seborrhœa and depilation are most marked outward signs of infection, being due to parasite-laden histiocytes around the hair follicles. Infected cells are found distributed uniformly in the dermis and throughout the unbroken skin of the entire body of dogs, so much so that any bloodsucking arthropod is bound to ingest infected cells from the skin juice in the act of feeding. This explains the high infection rate of *P. perniciosus* and *P. major* when fed on infected dogs. Workers in E. Russia, Tadjikistan (Bokhara) have found that the jackal (*Canis (Thous) aureus*) replaces the dog as reservoir host and that the insect intermediary is *P. arpaklensis* (Latyshev).

In Sicily and in Malta, Adler and Theodor found that both infantile and canine leishmania are transmitted by *Phlebotomus perniciosus*, and these insects can be infected by feeding them on dogs suffering from kala-azar. The aldehyde test is not so reliable as a means of diagnosis as in man. The rate of infection of dogs is: Algiers 7.1 per cent.; Tunis 1.8 per cent.; Lisbon 3.7 per cent.;

Malta 10 per cent.; Rome 16 per cent.; Messina 81 per cent.; Canea (Crete) 20 per cent.; Island of Hydra 17 per cent.

Other mammals.—In Morocco the Barbary ground squirrel (*Xerus getulus*) has been found naturally infected. In Brazil the Texas ground-squirrel (*Citellus tredecimlineatus*) has been found susceptible and *L. braziliensis* has been found in the paca (*Dinomys branicki*), a large rodent. The Chinese sand-hamster (*Cricetulus griseus*), susceptible to artificial infection, is a small species, 12 cm. in length and 30 grm. in weight. It has a range extending from Peking into Chinese Mongolia. Greyish-brown with median dorsal stripe, it has a short stumpy tail, lives in deep burrows, frequenting cornfields and destroying grain. The hamster of Syria, Palestine, Greece (*Cricetus auratus*) and the Macedonian spermophile (*Citellus citellus*), the European souslik, and other species of hamster (*C. accedula* and *Cricetus cricetus*) are very susceptible. In China, the mole rat (*Myospalax fontanieri*), the ground squirrel (*Citellus dauricus*); in Palestine, the field mouse, Guenther's vole (*Microtus guentheri*); in Sudan, the gerbille (*Gerbillus pygargus*) and the white-rumped gerbille (*Jaculus gordonii*); in Japan, a striped squirrel can be infected; in E. Russia and Turkmenistan the jackal is infected and various species of gerbille (*Palliosomys erythourus*). In Kenya these rodents (*Tatera vicina*) have now been found to be infected with *L. donovani* which, when inoculated into a volunteer, have reproduced the disease (Clinton Manson-Bahr). Heisch (1957) has also isolated the parasite from a ground squirrel (*Exerus erythropus*) in Kenya. A hamster was inoculated with the emulsified spleen. A year later the latter animal was found infected and had an enlarged spleen. Fulton and Niven have proved that the cotton rat (*Sigmodon hispidus*) is susceptible. Bolliger and Backhouse found that in Australian opossums (*Trichosurus vulpecula* and *Pseudocheirus laviginosus*), various eye lesions, conjunctivitis, interstitial keratitis and cataracts are produced. American marsupials (*Didelphis marsupialis* and *Metachirus nudicaudatus*) are susceptible.¹

Transmission of *L. tropica* also takes place through phlebotomus, and follows the same method of development as *L. donovani*. The infective forms of leishmania are inoculated by the bite of the sandfly, and the resulting sores have been experimentally reproduced by Wenyon in Iraq, the Sergeants in Algiers, by Adler and Theodor in Jerusalem, by the method of inoculating crushed infected sandflies or by feeding sandflies originally infected by ingestion of cultures. The species concerned in N. Africa and E. Mediterranean are *P. papatasi* and *P. sergenti*; in Iraq, India and Persia, *P. sergenti*; in Central Asia, *P. caucasicus*. In Brazil, N. Argentine and Paraguay, *L. braziliensis* is transmitted by *P. intermedius*.

Medium for culture of Leishmania.—This is made under aseptic conditions from the spleen of infected hamsters in a liquid medium consisting of 30 ml. of a solution (made from 1 litre of 0.9 per cent. NaCl + 20 ml. of 1.15 per cent. KCl + 2 grm. of glucose). To this after autoclaving are added 6 ml. of a mixture (100 ml. rabbit serum + 50 ml. of ox liver extract + 2 grm. Bacto-peptone dissolved in 10 ml. distilled water + 40 ml. hæmoglobin solution).

The pH is adjusted to 8.0–8.2 after which it is passed through a Seitz filter. In this medium cultures are subsequently maintained in serial passage every 6–8 days, but not for more than 25 subcultures, when intraperitoneal injection of hamsters has to be resorted to (Fulton and Joyner, 1956).

Nomenclature of hæmoflagellates.—Four types of flagellates are recognized:—Leishmania, Leptomonas, Crithidia, and Trypanosoma. Certain flagellates have leishmanial and leptomonad stages only. When confined to the intestinal tract of insects they are referred to the genus *Leptomonas*: in insects

¹ Guinea-pig leishmaniasis was discovered by Medina (1946) in S. Brazil and the parasite is *L. enriettii* (Munis and Medina, 1948). Primarily a cutaneous infection, it spreads through the body via the lymphatics.

as well as vertebrates to the genus *Leishmania*. Others again pass through leishmanial and crithidial stages, are confined to insects, and are classified as typifying the genus *Crithidia* (Fig. 274). Others again exhibit leishmanial, crithidial and trypanosomal stages. When found in insects alone they constitute the genus *Herpetomonas*, but if part of the life history is passed partly in insects, and partly in vertebrates, the parasite is then known as *Trypanosoma*.

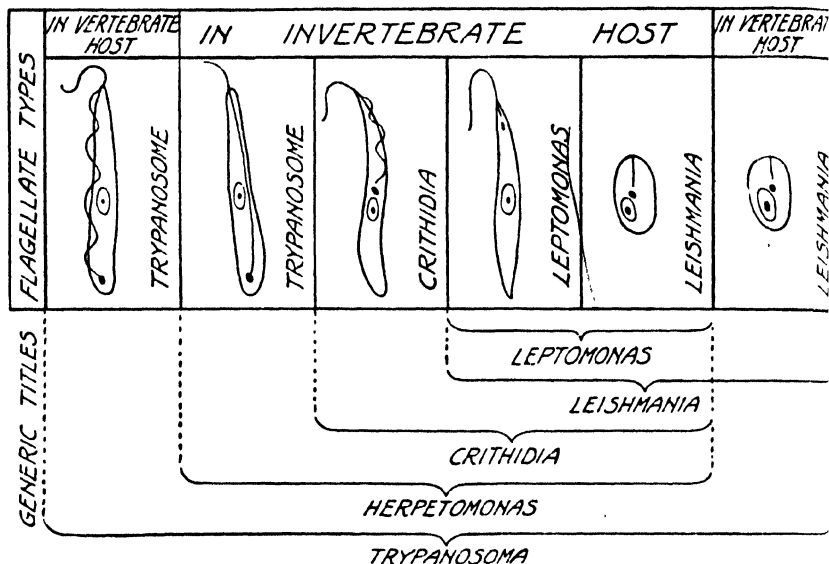


Fig. 274.-- Diagram illustrating relationships of various genera of blood and tissue flagellates and the morphology of the various developmental forms and species. (After Wenyon.)

PARASITES OF UNCERTAIN ORIGIN

TOXOPLASMA (Nicolle and Manceaux, 1908)

Toxoplasma is an intracellular protozoan (Fig. 275), of which the type is *Toxoplasma gondii*, first described in 1908 by Nicolle in a N. African rodent, the gundi (*Ctenodactylus gundi*). Almost simultaneously Splendore described a similar organism in rabbits in Brazil. The organism, as described by Olitsky, in guinea-pigs, was found within living cells, not only monocytes, but also every type of parenchymal cells, and infection could be produced experimentally by intravenous, intranasal and other routes. It is an obligatory intracellular parasite and all strains recovered from man and animals are morphologically and immunologically identical. In its free stage *T. gondii* is typically curved, or crescent-shaped, measuring 4-6 μ in length, 2-3 μ in breadth, with one end more rounded. When stained by Giemsa, the cytoplasm stains blue and the nucleus is a red, or purple, irregular mass occupying 1/5 or 1/4 of the cell and eccentric in position. In the intracellular stages *T. gondii* may appear singly or in clusters within the reticulo-endothelial cells and in this situation may readily be confused with leishmania. Clusters, or pseudocysts, have also been described. Reproduction is by longitudinal division. Its zoological status is still uncertain. This parasite is widespread in dogs, guinea-pigs, hares and pigeons throughout the world. It has

been found in mice, wild birds and in a monkey (*M. mulatta*), in rat, weasel, ferret and polecat (Lainson). The multimammate mouse (*Mastomys coucha*) is very susceptible to infection. Human infections have been reported from Europe, Middle East, Ceylon, North, Central and South America, Australia and Hawaii. In England the first case was described by Jacoby and Sagorin (1948).

Toxoplasmosis in man may be congenital or acquired. In mice the disease has been experimentally transmitted *in utero* as well as through the milk. Large scale dye and skin-test surveys have been conducted in various parts of the world and the results indicate that inapparent infection with toxoplasmosis is widespread. According to Beattie (1957) the incidence in the United Kingdom is about 1 : 35,000.

Clinical.—The most commonly clinical picture of human toxoplasmosis is the result of congenital infection in infants and young children. It usually appears as a form of encephalitis, accompanied by choroidoretinitis, hydrocephalus or microcephaly, microphthalmos, mental retardation and convulsions. Acute toxoplasmosis in adults is rare, frequently fatal and is usually accompanied by prolonged remittent fever. Often there is a maculo-papular erythematous rash which does not appear on the hands, feet or scalp. In recognition of the disease the syndrome of Sabin (1942) is an important tetrad of signs:—internal hydrocephalus, or microcephaly, choroidoretinitis, convulsions and evidence of cerebral calcification.

The cerebrospinal fluid is xanthochromic, under increased pressure, with high protein content and containing numerous mononuclear cells. Toxoplasms are found in films of centrifuged deposit and by animal inoculations. In the brain toxoplasma pseudocysts may be seen in apparently healthy tissue within a short distance from necrotic areas.

In the child the disease becomes obvious days or weeks after birth and choroidoretinitis is found in about 90 per cent. Hydro- or microcephaly is found in about half. Often ocular manifestations, such as nystagmus, strabismus, cataract, iritis, optic atrophy, may be found. The infection from the mother passes through the placenta late in pregnancy when any neutralization of antibody cannot take place. The child is usually born jaundiced with purpuric or maculo-papular rash, enlarged liver and spleen. In such a case naturally erythroblastosis foetalis is suspected. On the other hand, in congenital infections severe disease is the exception rather than the rule. Antibody surveys show that a large proportion of the population have been infected with toxoplasms at some time or other.

Siim (1951) found evidence of toxoplasmosis in febrile cases in three forms: in febrile lymphadenopathy, afebrile adenopathy and what is known as a subclinical form. Paulley, Jones and Green (1954) have actually suggested the possible toxoplasmic infection in cases of Fiedler's myocarditis and unexplained cardiomegaly associated with positive serological tests and abnormal electrocardiograms. They think that toxoplasmosis must be excluded in all forms of myocarditis and endomyocardial fibrosis.

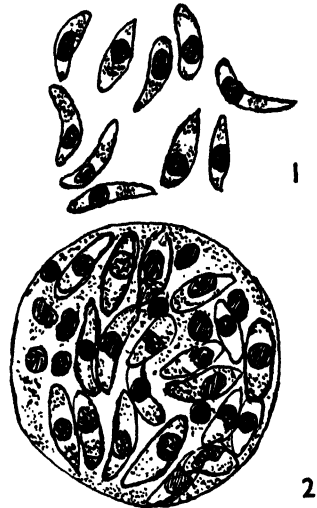


Fig. 275.—*Toxoplasma gondii*.
Types of Spore.

1. Various forms.
2. Group of spores resulting from schizogony.

(After Carini and Maciel, 1914.)

For *diagnosis* the skin-test of Frenzel is used; 0.1 ml. of 1 : 500 dilution of supernatant fluid from centrifuged frozen peritoneal exudate of infected Swiss mice, to which merthiolate in a dilution of 1 : 10,000 has been added. Injected intradermally, the test is positive when, after 24–48 hours, an areola persists which is larger than 0.5 cm. In congenital toxoplasmosis with meningo-encephalitis calcification, as ascertained by radiography, suffices to diagnose it soon after birth.

The slide neutralization test of Sabin and Feldmann consists of mixing equal parts of peritoneal exudate from infected mice and of the subject's serum, incubating at 37°C. for one hour, examining under a high-power microscope a drop of the mixture to which one drop of saturated solution of methylene blue has been added. In absence of antibody, 90–100 per cent. of toxoplasma take the stain, whereas in its presence less than 50 per cent. are stained. A complement-fixation test is that of Warren and Sabin. The antigen consists of the clear supernatant fluid obtained by centrifugation of pooled infected mouse peritoneal exudate, macerated by alternate freezing and thawing.

Treatment at present is unsatisfactory. Patencia claims that tetracycline is the only drug and it has been used in experimental toxoplasmosis by Nobrega and Giovanni. Wettingfield, Rowe and Eyles (1956) claim that the best results

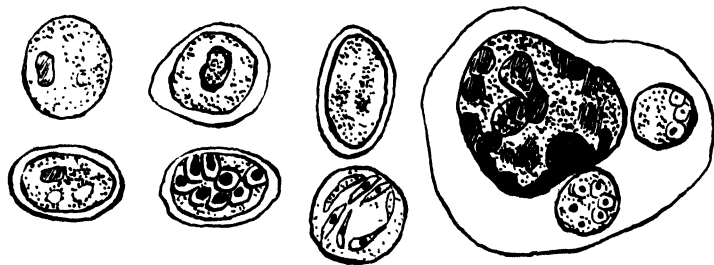


Fig. 276.—*Pneumocystis carinii* from the lung smear of a dog.

(After Carini and Maciel, 1914.)

so far have been obtained with sulphonamides and pyrimethamine (Daraprim). The latter was given in an initial dose of 50 mgm. followed by 50 mgm. in six hours and 25 mgm. thereafter daily for 14 days. (This treatment was carried out successfully in a laboratory technician who contracted toxoplasmosis.) Quite recently Perkins and colleagues (1956) have reported favourably on pyrimethamine in the treatment of toxoplasmic uveitis. The dose was 25 mgm. daily for four weeks. The improvement rate was 76 per cent. and 88 per cent. in those with posterior uveitis. The only apparent side-effect was some depression of erythropoiesis (Beverley, 1957).

PNEUMOCYSTIS

Pneumocystis carinii (Fig. 276) was first described by Chagas in 1909, and again in 1911, later by Carini and Maciel in 1915 in the lungs of guinea pigs. At first the organism was thought to represent a stage in the life-cycle of *Trypanosoma cruzi*. Later Delanoe found it in the lungs of rats and was then named *carinii* (Wenyon). Meer and Brug, in 1942, first suggested that it might be a pathogenic parasite of man. The cycle in the lungs was described by Vaněk in 1953. Together with Jiróvec (1952) he described the pathology of the disease known as "Parasitic Pneumonia" or "Interstitial Plasma-cell Pneumonia" in infants. The disease invariably takes a fatal course. The parasites are at first uni-

nucleated roundish or longish bodies reproducing by binary fission and forming eight germinal sporogonies, 5–7 μ in size. The *pneumocystis* forms foamlike masses which are composed of parasites in alveoli and bronchioles of the lung. Domestic animals, rabbits, guinea-pigs, cats, dogs, sheep and goats form the reservoirs of infection. The mode of transmission is unknown. The majority of cases so far reported are from Yugoslavia, from Germany (Westphal) and more recently from N. America and Chile (Dauzier and Pizzi, 1956). *P. carinii* has been found in adults with pneumonia associated with Hodgkins' disease, myeloid leukaemia and cytomegalic inclusion disease.

SUBCLASS SARCOSPORIDIA

Genus: *Sarcocystis*

Sarcosporidia are parasites which inhabit the muscular and connective tissues of vertebrates. They are elongated, sausage-shaped bodies with a cuticle within which are enclosed a number of falciform spores ("Rainey's corpuscles"). *Sarcocystis* produces a substance—"sarcocystine"—which is especially toxic for the rabbit. The cysts, which are visible to the naked eye, are commonly known as Rainey's or Miescher's tubes; they are frequently found in animals, but rarely in man in whom they have been recorded from the myocardium, larynx and arm muscles.

The species in man is *Sarcocystis miescheriana* (*S. lindemanni*). There are authentic cases on record. Lindemann (1868) found it in heart-muscle; Baraban and St. Remy (1894) in laryngeal muscles; Darling (1909) in the biceps of a negro; Manifold (1924) again in the myocardium. Mackinnon and Abbott (1955) found one in the muscles of the foot of a Sudanese suffering from madura foot.

THE SPIROCHÆTES

GROUP: SPIROCHAETACEA

Genus: *Spirochæta* (*Treponema*)

Genus: *Leptospira*. Genus *Spirillum*

These organisms, whose exact status in the scheme of nature is indeterminate, are included as a matter of convenience. They are now regarded as being nearer to plants than to animals, though formerly, on account of the method of transmission of blood-inhabiting species by lice and ticks, they were formerly classified as protozoa. Amongst spirochætes which deserve consideration in this work are: *Spirochæta pallida* (Fig. 277, 5) of syphilis; the corresponding closely-allied organisms of yaws, *S. pertenue*, and of pinta, *S. carateum*. The organisms are small, 5–14 μ in length, and are composed of numerous regularly disposed corkscrew-like spirals of an amplitude of 1 μ . The extremities are pointed, the spirals wavy and regular. By aid of the electron microscope they are seen to possess flagella, and possibly an undulating membrane. Distinction can be drawn between two types of relapsing fever spirochætes: one transmitted by lice, the other by ticks. Rodents are well known to be reservoirs of the latter, but play no part in the maintenance of louse-transmitted strains.

Somewhat similar non-pathogenic species are found in the mouth (*S. dentium*), throat (*S. vincenti*) and bronchi (*S. bronchialis*). These organisms have been held responsible for "bronchial spirochætosis." Other somewhat similar species are found in the intestine (*S. eugyrate*) and were once thought to give rise to "spirochætal dysentery." Larger species with wider curves are recognized on ulcerating surfaces—*S. refringens*, *S. gracile* on the external genitalia, and *S. schaudinni* in tropical ulcers.

The larger forms of *spirochæta* are more flexible and snake-like. They comprise

the pathogenic blood spirochætes, the organisms of relapsing fever (*S. recurrentis* (Fig. 277, 4), *S. duttoni*, *S. sogdianum*, *S. hispanica*, and other allied forms). In birds (geese and fowls) similar parasites cause a fatal blood disease. The organisms are *S. anserinum* and *S. gallinarum* respectively.

The human blood spirochætes are transmitted by ticks (*Ornithodoros*) or by lice (*Pediculus*); those of birds also by ticks (*Argas*). All these spirochætes progress by corkscrew action resulting from revolution on the longitudinal axis.

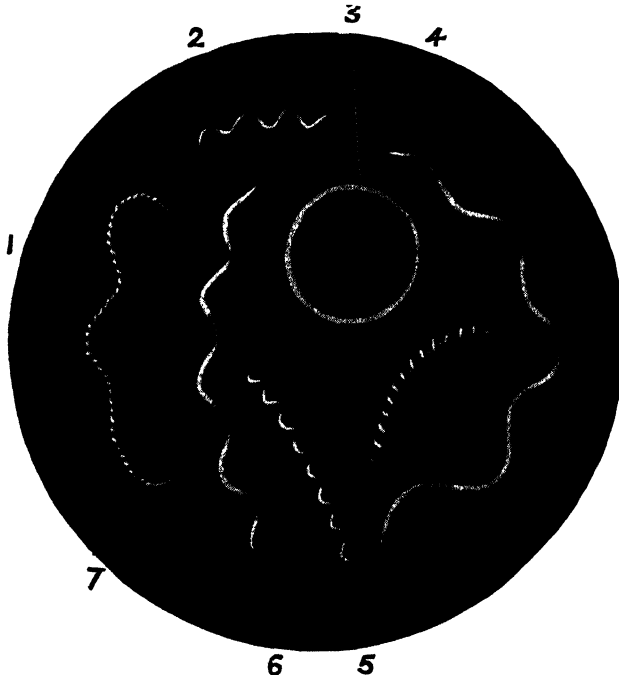


Fig. 277.—Schema of different forms of spirochætes. $\times 3,500$.

(After Dobell; by courtesy of Wellcome Bur. Sci. Res.)

1. *Leptospira icterohæmorrhagiae* (Inada and Ido) Noguchi. Cause of spirochætal jaundice.
2. *Spirochæta eurygyrata* Werner. Commonly found in human faeces, both in health and in disease. (e.g. dysentery).
3. Human red blood-corpuscle on same scale.
4. *Spirochæta recurrentis* Leber (= *Spirochæta obermeyer* Cohn). Occurs in blood in relapsing fever.
5. *Spirochæta pallida* (Schaudinn) Vuillemin (= *Treponema pallidum* Schaudinn). Syphilis.
6. *Spirochæta gracile* Ievaditi and Stanesco. Found on external genitalia, in health and in various diseased conditions.
7. *Spirochæta refringens* Schaudinn (emend.). Occurs in syphilitic lesions on external genitalia.

Genus: *Leptospira*

Leptospira (Noguchi, 1917) includes the type *Leptospira icterohæmorrhagiae* (Fig. 277, 7). These organisms measure 7–14 μ in length, with pointed ends and a spiral amplitude of 0.45 μ , and exhibit one or more gently undulating curves. There is no terminal axial filament or undulating membrane, but usually the end is bent inwards in the form of a crook. Two main pathogenic species (with variant forms) are recognized: *L. icterohæmorrhagiae* of Weil's disease, and *L. hebdomadis* of seven-day fever. *L. icterohæmorrhagiae* infests

the urinary tract and liver of rats, and may possibly also occur as a free-living form in water (Zuelzer). It has also been found in the roof-slime of a mine in Scotland (Buchanan). It is highly pathogenic to guinea-pigs. *L. canicola* is found in dogs and is transmitted to man, especially in Holland. *L. hebdomadis*, on the other hand, occurs as a natural infection in the field-vole—*Microtus montebelloi* in Japan: *L. pomona* is found in pigs.

The spirochaetes reproduce by simple transverse fission. No sexual phenomena have been observed in any spirochaete and the life-histories of all are simple. Some observers have held that spirochaetes have a granular phase during which they break up into minute granules which are capable of regenerating into spirochaetes.

Genus: *Spirillum*

The organism of rat-bite fever—formerly *Spirochaeta morsus muris* (p. 201)—is no longer classified as a spirochaete but as a *spirillum*. The correct terminology should be *Spirillum minus* (Carter, 1887). The synonyms therefore are: *Spirochaeta laverani* and *Spirochaeta muris* (Wenyon, 1906).

INTESTINAL AMOEBAE

Class: RHIZOPODA. Family: ENTAMOEBIIDÆ. Genus: ENTAMOEBA.
Entamoeba histolytica (SCHAUDINN, 1903). SYNONYM *Entamoeba dysenteriae* (FIG. 278)

Individuals of *E. histolytica* vary in size; usually the active forms are 20–30 μ in diameter; when active, they push out characteristic hyaline pseudopodia. The movements are in one direction, causing the protoplasmic mass to glide

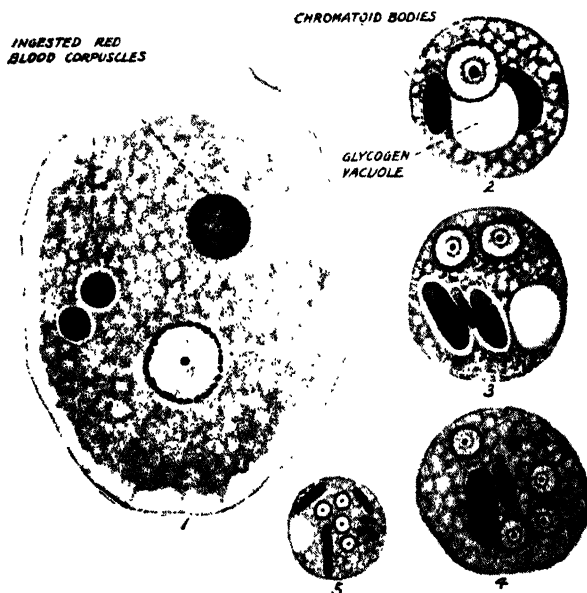


Fig. 278.—*Entamoeba histolytica*. $\times 2,500$. (After Dobell.)

- 1 Active ameboid form with ingested red blood-corpuscles. 2, Uninucleate cyst. 3, Binucleate cyst.
- 4 Quadrinucleate cyst. 5, Quadrinucleate cyst, small race, 6.6 μ in diameter. Note central distinct karyosome in the nucleus.

across the microscope stage like a "slug moving at express speed." (Fig. 83, p. 464.)

The *cytoplasm* is divisible into two zones: outer, with clear ectoplasm; inner, granular endoplasm.

The *nucleus* (4–7 μ in diameter) is usually invisible in the living state; when stained it shows a dot-like small central karyosome and peripheral chromatin in the form of fine granules; the nuclear membrane is a clear area marked by radial linin network.

Vacuoles are not present in active living individuals, but in degenerating trophozoites.

Large active entamoebæ, vegetative or tissue-invading forms, are found in the intestinal wall, mainly in tissues at the bases of ulcers, where they multiply by *binary fission*, ingesting erythrocytes, leucocytes and tissue cells. The practical issue to the recognized fact that active amœbæ in faeces containing ingested red blood corpuscles are most certainly *E. histolytica*. The forms produced in culture will readily engulf erythrocytes in a test tube. It is also claimed that *E. coli* will do the same, but this never occurs under natural conditions. These are the main distinguishing features between *E. histolytica*, *E. coli* and other non-pathogenic species. Further, in contrast to *E. coli*, *E. histolytica* rarely ingests bacteria. Tissue-invading forms represent the most active phase of development. They are normally found in the walls of the intestinal ulcers, in dysenteric faeces, and in metastatic lesions in lung, liver or other organs.

Amœbic dysentery can be transmitted to kittens, dogs, guinea-pigs, monkeys and rats. Amœbic hepatitis has been produced in hamsters (*Cricetus auratus*) by Reinertson and Thompson (1951). Jones (1946) and Goodwin (1947) have reproduced typical amœbic ulceration of the cæcum of young white rats by intracæcal injection of cultures of *E. histolytica* and also by injecting dysenteric stools of artificially infected kittens. Ulceration becomes evident in 24 hours. Carrera and Faust find guinea-pigs are easily infected by intraileal injection. Tobie has infected rabbits by intrasophageal inoculation. Though closely resembling *E. muris*, the common parasite of the rat, this animal has been found naturally infected with *E. histolytica* in U.S.A., Russia, and now in wild rats in London, in close association with human carriers of *E. histolytica* cysts (Neal). The importance of this subject has recently been re-emphasized by the same author (1951), who has adduced further evidence that the sewer-rat, *R. norvegicus*, plays a prominent part in the dissemination of amœbic dysentery. Amongst all hosts the dog is unique, for when infected with a "carrier" strain and on a normal diet no clinical symptoms appear, but if the diet is changed to salmon, the infection becomes acute and amœbic lesions are found at autopsy. From a study of the behaviour of *E. histolytica* in this rodent as well as in man, Hoare now believes that *E. histolytica* can no longer be regarded as an obligatory tissue-parasite; but that it also has a saprophytic coprozoic existence living as a commensal in the lumen of the gut, feeding on micro-organisms and other faecal contents. As shown by Hoare a fair proportion of the entamoebæ contain food-vacuoles enclosing bacteria. This explanation tallies with clinical experience in symptomless cyst carriers whom it is easy to cure of this infection with drugs which exert no influence on the tissue-invading forms. There appears to be every gradation between these two stages in rats as well as, probably, in man.

According to Hoare, the virulence of *E. histolytica* depends upon its capacity for invading the mucosa—a capacity which also varies. Thus, as a general rule, rats infected with a "carrier" strain show no ulceration and those from acute cases produce acute lesions. Liver-passaged cultures treated with streptomycin, in order to modify the bacterial flora become attenuated. The invasiveness of avirulent strains cannot be increased experimentally.

Precystic forms.—Precystic forms develop from the larger entamoebæ by division, giving rise to small daughter-amœbæ. These are sluggish, with cytoplasm devoid of food vacuoles, and vary in size from 5 to 20 μ . The "*minuta*" forms, 12–14 μ , are smaller than the tissue-invading form. They ingest bacteria and resemble a similar stage of *E. coli*. The presence of food inclusions distinguish them from precystic amœbæ. "*Minuta*" forms hatch out normally from the large race of *E. histolytica* living commensally in the faeces.

Cysts.—Cysts of *E. histolytica* in fresh material have a greenish refractile appearance. Sometimes on this account it is difficult to distinguish the nuclei, though chromatoid bodies may be clearly seen. It appears that there are two races: small, with mean diameter of cyst 7 μ ; large up to 11 μ . The small (*E. hartmanni*) is considered non-pathogenic, whilst the large race is distinctly pathogenic. The small race (*E. hartmanni*), from which small trophozoites hatch, may be mistaken for *minuta* forms. (Fig. 278, 2–5.) The mature cyst of *E. histolytica* is quadrinucleate and commonly contains within its cytoplasm refractile chromatoid bodies. The cyst at first contains one, then two, and finally four nuclei, which retain the *E. histolytica* characteristics. A glycogen mass is also present, showing up brown with iodine, but both these features gradually disappear after the cysts have been voided in the faeces.

Mature cysts do not undergo any further development in the intestine and, under normal conditions, do not hatch there, but acute infection of kittens can be readily produced by intra-rectal injection of material containing them. The process of conversion of the precystic form to the fully-mature cyst takes place in the lumen of the bowel and occupies a few hours. The quadrinucleate cysts can survive in the bowel for two days, but do not hatch until ingested by a new host. It has been suggested that some substance is present preventing further development. Fluid is apparently necessary for excystation; but from the quadrinucleate cyst a quadrinucleate amœba emerges, subsequently dividing by nuclear mitosis into eight unicleated individuals. This normally takes place when cysts are swallowed by a new host. The composition of the cyst wall renders it impervious to the action of the gastric juice, and excystation normally takes place in the alkaline contents of the small intestine. The generally accepted method of determining vitality of cysts is their capacity for taking up eosin-stain. Dead cysts stain with weak eosin solutions, whilst living cysts do not.

Entamoeba hartmanni. Von Prowazek, 1912.

The small race (*E. hartmanni*) differs from the large one in the following characteristics: (a) both trophozoites and cysts are smaller; (b) like the commensal (*minuta*) forms of the large race they are restricted to the lumen of the gut and do not invade the tissues. If this subject is not sufficiently complex, there are some who claim that *E. histolytica* itself possesses a dwarf strain, similar to *E. hartmanni* in size, but differing from it in structure (Burrows, 1957). The nucleus is relatively larger, in relation to the cyst in *E. hartmanni*, and the glycogen masses are smaller. There is said to be some difference in the arrangement of chromatin in the nucleus (Burrows and Brooke, 1958).

Random measurements of *E. histolytica* provide no clue to the variation in this species. It may be produced experimentally, or they may be genetically fixed, as in the case of the large and small races. In the latter case the persistence of a bimodal curve provides a good criterion for the differentiation of *E. histolytica* from *E. hartmanni*. Separation of the larger species from the smaller one is based on a mean size of 10 μ for cysts and 12 μ for trophozoites, measurements which can serve as a dividing line.

Culture.—Cultivation of *E. histolytica*, in either active or cystic stage, on artificial media, can be effected on solidified egg slopes covered with horse serum

PLATE XXIV

INTESTINAL PROTOZOA (Unstained)

Row A. *Entamæba histolytica*.

- 1.—Active vegetative form with ingested red blood-corpuscles: granular endoplasm and clear ectoplasm.
- 2.—Precystic form: note large nucleus with central karyosome.
- 3.—Immature cyst with two nuclei and contained chromatoid rods.
- 4.—Mature cyst with four nuclei, vacuole and chromatoid rods.
- 5.—Uninucleated cyst of the minute form.

Row B. *Entamæba coli*.

- 1.—Active vegetative form with characteristic nucleus, blunt pseudopodium and protoplasmic vacuoles with food material.
- 2.—Precystic form with characteristic nucleus.
- 3.—Immature stage with two nuclei and vacuole.
- 4.—Mature cyst with eight nuclei.

Row C. *Endolimax nana*.

- 1.—Active vegetative form with one nucleus and many small vacuoles.
- 2.—Mature cyst with four nuclei.

Iodamæba bütschlii.

- 3.—Active vegetative form with one nucleus and vacuoles.
- 4.—Mature cyst with one nucleus and large vacuole.

Row D. *Giardia intestinalis*.

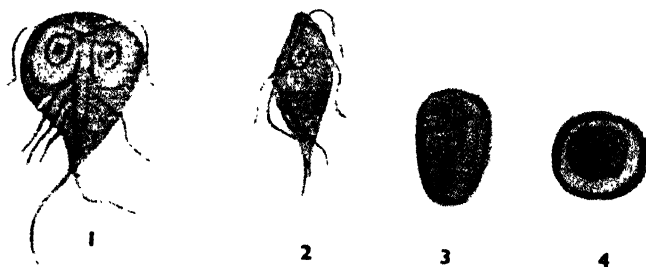
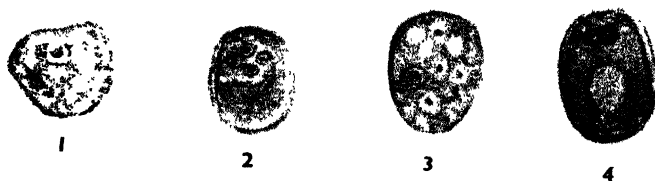
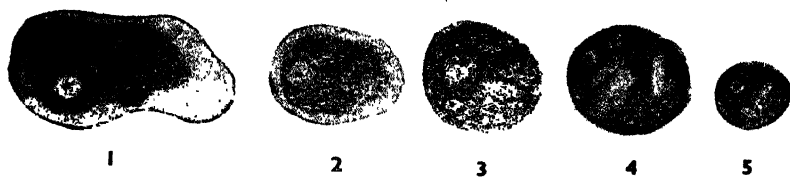
- 1.—Active form with sucking disc.
- 2.—Active form (side view).
- 3.—Cyst with four recently divided nuclei.
- 4.—Four nucleated cyst (end-on view).

Row E. *Trichomonas hominis*.

- 1.—Active form with undulating membrane and supporting rod.

Chilomastix mesnili.

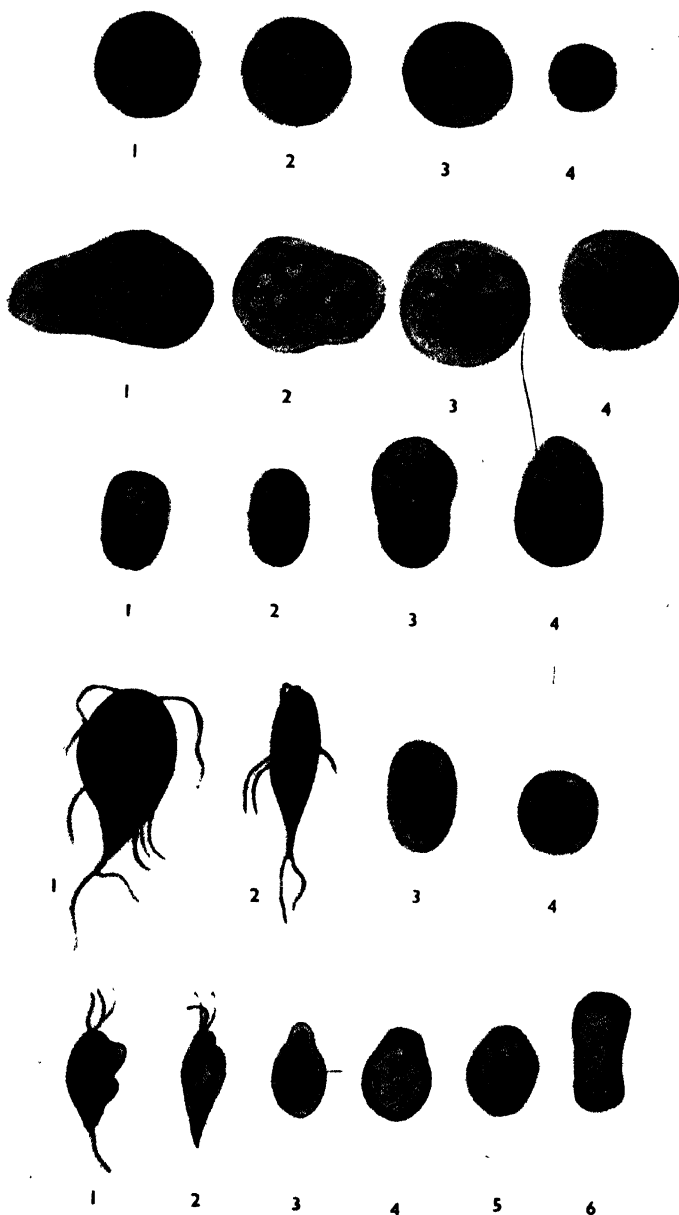
- 2.—Active form with peristome and contained flagellum.
- 3.—Pear-shaped cyst of above.
- 4, 5, 6.—Various forms of *Blastocystis hominis*.



HUMAN INTESTINAL PROTOZOA (unstained)

(P. Manson-Bahr)

PLATE XXIV



HUMAN INTESTINAL PROTOZOA (stained with Weigert's iodine)

(P. Manson-Bahr)

PLATE XXV

PLATE XXV

INTESTINAL PROTOZOA (Stained Weigert's Iodine)

Row A₁. *Entamæba histolytica*.

- 1.—Precystic form. Note diffuse iodine-staining substance.
- 2.—Immature cyst with two nuclei and chromidial rods.
- 3.—Mature cyst with four nuclei, iodine vacuoles and chromidial rods.
- 4.—Quadrinucleated cyst of the minuta form.

Row B₁. *Entamæba coli*.

- 1.—Active vegetative form with vacuoles and ingested food material.
- 2.—Precystic form.
- 3.—Immature cyst with two nuclei and vacuole.
- 4.—Mature cyst with eight nuclei.

Row C₁. *Endolimax nana*.

- 1.—Active vegetative form with one nucleus and protoplasmic granules.
- 2.—Mature cyst with four characteristic nuclei and iodine-staining substance.

Iodamæba bütschlii.

- 3.—Active vegetative form with one nucleus and iodine-staining vacuoles.
- 4.—Mature cyst with one nucleus and iodine-staining vacuole.

Row D₁. *Giardia intestinalis*.

- 1.—Active form with sucking disc.
- 2.—Active form (side view).
- 3.—Cyst with four recently divided nuclei.
- 4.—Four nucleated cyst (end-on view).

Row E₁. *Trichomonas hominis*.

- 1.—Active form with undulating membrane.

Chilomastix mesnili.

- 2.—Active form with peristome and contained flagellum.
- 3.—Pear-shaped cyst of above with nucleus and peristome.
- 4, 5, 6.—Various forms of *Blastocystis hominis*.

and Ringer's solution. The addition of a small quantity of rice starch to each tube greatly aids the growth of amœbæ, which ingest the granules. The cultures are kept at 37° C. and should be re-inoculated every two to four days. Subcultures have been maintained for one hundred and fifty generations and are still capable of producing amœbic dysentery when injected into kittens. The student should bear in mind that the appearance of amœbæ in culture is somewhat altered by the starch granules they contain. Fuller and Faust demonstrated that dilution of aureomycin less than 1 : 100,000 inhibits the growth of *E. histolytica*, and checks the growth of bacteria. It is concluded that this amœba grows in aureomycin as well as in penicillin or streptomycin cultures.

If starch is withheld from the cultures, if, in subsequent cultures, fresh blood is introduced, the amœbæ ingest red blood-corpuscles. Cysts in faeces stored at 4–6° C. remain viable and culturable as long as fifteen days. According to Dobell, symbiosis exists between amœbæ and a bacterium which is necessary for encystment (*convivium*). *E. histolytica* in culture is extremely sensitive to emetine, which destroys them within four days in the strength of one in five million. Amœbiasis may be reproduced in cats, dogs and rhesus monkeys (*Macaca mulatta*) and to a lesser extent in the guinea-pig, rabbit and rat, by injection of cultures. An amœba naturally found in anthropoid apes, macaques and other monkeys is probably identical with the human species. *E. ranarum* of the frog is morphologically identical. Amœbic dysentery in the kitten is severe and *E. histolytica* cysts are never produced. The mucosa of the whole of the large intestine is affected, and, in animals that survive, bacterial infection of the bloodstream, derived from the intestine, ensues. Metastatic amœbic abscesses of the liver are not infrequent in the cat, rarely in the dog.

Propagation of *E. histolytica* has been obtained in tissue culture without accompanying bacteria (Shaffer, Sienkewicz, 1953). It grows best under anaerobic conditions and in the tissues of older chick embryos better than in younger ones. Good results are attained by cultivating *E. histolytica* with living or killed *Trypanosoma cruzi*. These are grown in microtubes (4 × 50 mm.) in a medium of thioglycollate preparation, horse serum and an overlay of N.I.H. medium containing a rich culture of trypanosomes. Culture of the amœba, grown in thioglycollate-serum medium in the presence of penicillin-inhibited streptobacilli are inoculated into test-tubes with the preceding medium containing *T. cruzi*. The amœbatrypanosome cultures are maintained in 15 passages of subinoculation at intervals of 48 hours; penicillin being added to ensure elimination of the streptobacillus. Microcultures of *E. histolytica* are started from single washed amœbæ which are transferred by micro-isolation to microtubes containing the above medium with trypanosomes, and in these cultures active amœbæ can be seen for ten days.

Rees, Reardon and Bartgis (1950) have shown that *E. histolytica* is capable of hatching from cysts in the absence of bacteria only when complex organic substances are added to the medium. Excystation proceeded very slowly in inorganic media without bicarbonates, was moderate in inorganic fluids with bicarbonates in glucose, but was best in media with bicarbonates and all organic compounds. The presence of amino-acids is essential. The cysts of *E. histolytica* cannot withstand drying. The cyst wall consists of one layer, measuring about 0.5 µ in diameter.

E. moshkovskii (Tshalaia, 1941). This species resembles *E. histolytica* in both trophozoite and cystic stages and has been recovered from sewage in Moscow, U.S.A., England and Brazil. Attempts to infect laboratory animals have been unsuccessful. *E. invadens*, a parasite of snakes, is also morphologically identical with *E. histolytica*.

ENTAMOEBA COLI

(GRASSI, 1879). (Fig. 279)

Unlike *E. histolytica*, this amoeba does not invade tissues ; it is therefore a non-pathogenic species and a harmless commensal in the intestinal tract of man. A similar amoeba is found in monkeys and rats.

E. coli is a very common parasite in the tropics and, wherever sanitation is primitive, it is probable that no individual escapes infection. On the average, *E. coli* is larger than *E. histolytica*, but varies greatly. The active vegetative stage measures from 10 to 40 μ , but is usually 20–30 μ in diameter. It normally lives in the large intestine, does not invade tissues, but develops in intestinal contents, where it ingests bacteria, yeasts and other material.

Generally speaking, movements are much more sluggish than those of *E. histolytica*, and the individuals are less active. The organism does not move across the slide, but remains stationary. The ectoplasm is not clearly defined but is represented by a superficial clearer area merging into the endoplasm

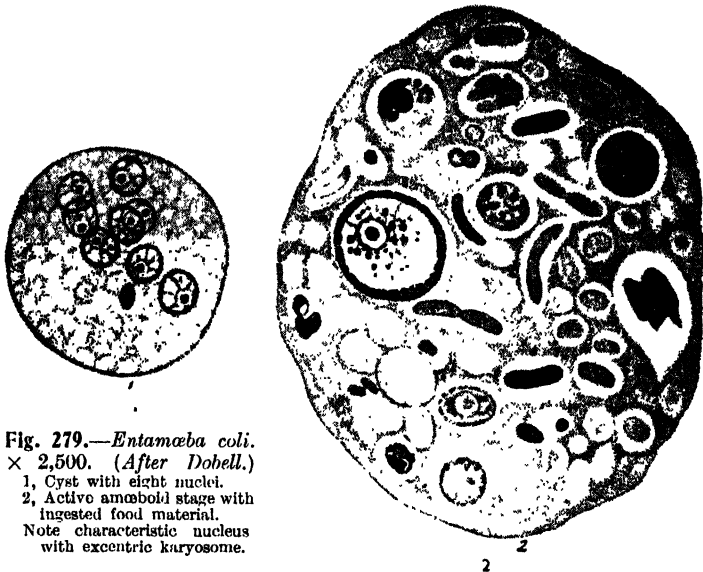


Fig. 279.—*Entamoeba coli*.
 $\times 2,500$. (After Dobell.)

- 1, Cyst with eight nuclei.
 - 2, Active amoeboid stage with ingested food material.
- Note characteristic nucleus with excentric karyosome.

This is extensively vacuolated, and food vacuoles contain bacteria, yeasts or even cysts of other protozoa, such as *E. histolytica*, *Giardia* and *Isospora*. Red blood corpuscles or tissue elements are not ingested. In general, *E. coli* is faintly grey, contrasting with the greenish tint and higher refractive index of *E. histolytica*. Sometimes individuals show various fissures or rectangular vacuoles representing degenerative changes.

The nucleus, compared with that of *E. histolytica*, is larger, coarser and more easily visible in the living organism (Fig. 279, 2). The chromatin granules on the nuclear membrane are relatively coarse, and there are others on the linin network. The karyosome, larger than that of *E. histolytica*, is usually eccentric in position, surrounded by a clear area intersected by linin network with chromatin granules. These nuclear characteristics are best seen in fresh specimens, but are obscured in degenerate individuals. *E. coli* reproduces by binary fission.

TABLE XI.—DIFFERENTIAL CHARACTERS OF THE COMMONER INTESTINAL AMŒBÆ

<i>Entamœba coli.</i>	<i>Entamœba histolytica.</i>	<i>Endolimax nana.</i>
Size: 10–40 μ .	20–30 μ .	6–12 μ .
Morphology: No distinction between endo- and ecto-plasm.	Granular endoplasm; clear ectoplasm.	Granular and rather vacuolated cytoplasm.
Ingests bacteria, other protozoa, etc.	Ingests red cells, tissue cells, etc.	Ingests bacteria and food granules.
Nucleus distinct in fresh specimens. Coarse chromatin granules on nuclear membrane. Eccentric karyosome surrounded by coarse ring.	Nucleus inconspicuous in fresh specimens. Fine chromatin granules on nuclear membrane. Central karyosome surrounded by delicate ring.	Clear nuclear membrane massive, irregular yosome.
Sluggish movement with granular pseudopodia.	Active movement with clear, blunt pseudopodia.	Sluggish movement with clear pseudopodia.
Multiplication: By binary fission in faeces. Encystment and formation of 1, 2, 4, and 8 nucleated spherical cysts, 10–30 μ in diameter.	By binary fission in intestinal wall. Encystment and formation of 1, 2, and 4 nucleated spherical cysts, 7–15 μ in diameter.	By binary fission in faeces. Encystment and formation of 1, 2, and 4 nucleated oval cysts 8–10 μ in length by 4–5 μ in breadth.
Chromatoid bodies typically not present in the mature cyst.	Chromatoid bodies especially present in the mature cyst.	Chromatoid bodies not present in the cyst.

Precystic forms.—Before encystment the amœbæ undergo reduction in size, with the result that precystic forms are especially difficult to distinguish from those of *E. histolytica*, but are usually larger. Precystic forms are probably formed by division of larger individuals.

Cysts (Fig. 279, 1).—The cyst wall is secreted round a spherical precystic amœba. Individual cysts vary greatly in size, from 10 to 30 μ . Like *E. histolytica*, *E. coli* is a composite species consisting of a number of races distinguished by the dimensions of the cysts.

The cyst is at first uninucleate, the nucleus having the same characteristics as that of the active form. It divides repeatedly by mitosis, the nuclei progressively diminishing in size as their number increases. The quadrinucleate stage is passed through very rapidly and is therefore rarely seen. The mature cyst is typically octonucleate. Immature binucleate and quadrinucleate cysts are occasionally seen, even supernucleate cysts with sixteen nuclei. The binucleate cyst frequently contains a large quantity of glycogen, which replaces almost the entire cytoplasm, but this usually disappears before the quadrinucleate stage is reached.

Chromatoid bodies are usually not present, but, when they are, they appear as small granular, spicular or rod-like bodies, more especially in the binucleate

stage. In the mature octonucleate form they may occasionally be seen as pointed threads or splinters, thus differing from the stouter bodies with blunted ends common in *E. histolytica*. When hatching, an octonucleate amoeba escapes from the cyst and gives rise to eight uninucleate amoebulae.

The life history of *E. coli* resembles that of *E. histolytica*, except that the vegetative forms inhabit the faeces, instead of the tissues of its host. This protozoan may be cultivated, but with difficulty, on the same media as are employed for *E. histolytica*. It is not affected by emetine. Cysts of *E. coli* can withstand drying while those of *E. histolytica* cannot. The cyst wall consists of two layers—a thick inner and a flexible outer wall measuring $1.0\ \mu$ in diameter.

Incidence.—*E. coli* is common in man in temperate zones as well as in the tropics, and found in about 15 per cent. of normal people. It is most readily seen in dysenteric cases with diarrhoea. Some monkeys harbour a parasite closely resembling it.

E. polecki (Von Prowazek, 1912), an intestinal amoeba of the frog and rhesus monkey has been reported from man in California. The trophozoite resembles *E. coli* in viscosity and movements.

Entamoeba gingivalis (Gros, 1849) (Fig. 280).

This amoeba is of interest, not only for its occurrence in the mouth, but also because it was the first to be discovered in man. The claim that it might prove to be the cause of pyorrhoea alveolaris has been disproved. This species has been found in pulmonary suppuration by Sutliff and others (1951) by bronchoscopy. The importance of this lies in its differentiation from *E. histolytica*.

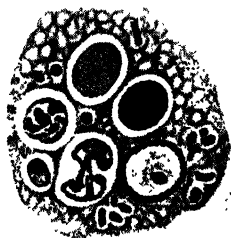


Fig. 280.—*Entamoeba gingivalis*: active amoeboid form with eccentric nucleus and ingested bodies. $\times 2,500$. (After Dobell.)

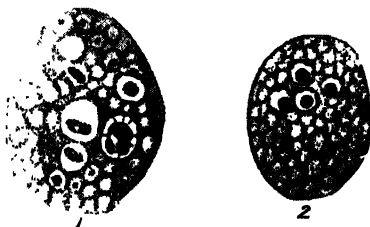


Fig. 281.—*Endolimax nana*. $\times 2,500$. (After Dobell.)

1, Active amoeboid form. 2, Quadrinucleate mature cyst.

E. gingivalis is a small species with great variations in size, from 10 to $25\ \mu$ depending on its metabolic activity. As in *E. histolytica*, endoplasm and ectoplasm are sharply differentiated. The cytoplasm is occupied by food vacuoles, and peculiar inclusions of a greenish refractile appearance of undetermined nature, which may be the remains of salivary corpuscles or polymorphonuclear cells; there are also numbers of ingested bacteria.

The nucleus is similar to that of *E. coli*. It is $2.5\text{--}3\ \mu$, spherical and vesicular, but slightly smaller in proportion to the rest of the organism than in *E. histolytica* or *E. coli*. The nuclear membrane is a definite structure, and is lined with peripheral chromatic granules.

E. gingivalis probably reproduces by binary fission, although all intermediary stages have not been studied and it is probable also that it does not form cysts.

Endolimax nana (Wenyon and O'Connor, 1917) (Fig. 281).

Genus: *Endolimax*.

This is a non-pathogenic species commonly inhabiting the intestinal tract of man (mainly of the large and to a lesser extent of the small intestine), especially in the tropics, and it is of importance because the spherical quadrinucleate cysts resemble those of the small race of *E. histolytica*; moreover, it is found in 33 per cent. of dysenteric or diarrhoeic faeces, and is often very abundant indeed.

E. nana is a small species, 6–12 μ in diameter; it has a characteristic vesicular nucleus with a large irregularly-shaped karyosome. It ingests food granules and bacteria, but not red blood corpuscles or cells. Its movements are sluggish, but it may become quite active on a warm stage.

The cysts (Fig. 281, 2) are of approximately the same size and appearance as the active form. When fully mature they have characteristic nuclei and contain a few refractile granules, but are devoid of vacuoles or chromatoid bodies. Sometimes they contain glycogen, especially the binucleate forms. In shape they vary from that of a typical oval to a sphere. Small individuals measure 6 μ in diameter. Occasionally, they contain small filamentous rods or granules.

E. nana is certainly non-pathogenic and is not amenable to emetine. This species has been successfully cultured on serum and egg media.

Iodamoeba bütschlii (Prowazek, 1912) (Fig. 282).

Genus: *Iodamoeba*.

Cysts of this species have long been known in man as "iodine," or "I. cysts," whilst similar organisms are found in the faeces of monkeys and pigs.

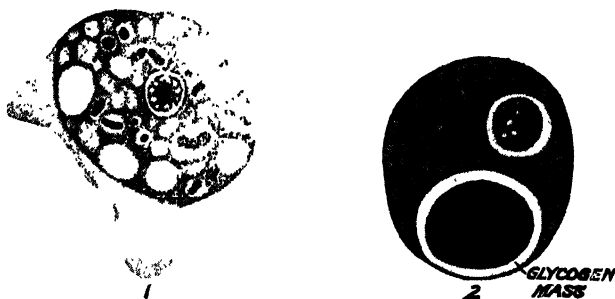


Fig. 282.—*Iodamoeba bütschlii*. $\times 2,500$. (After Dobell.)

1, Active amoeboid form with ingested micro-organisms. 2, Mature cyst, "iodine cyst," containing large iodine-staining glycogen mass.

I. bütschlii is small, intermediate in size between *E. coli* and *E. nana*, measuring from 9–20 μ in diameter, though smaller individuals, 5 μ in size, may occur. In form and habit it resembles small specimens of *E. coli*. The cytoplasm contains food vacuoles with bacteria and other food particles. There is no marked differentiation of ecto- and endoplasm. The movements are sluggish, like those of *E. coli*.

The nucleus, which is often indistinguishable in specimens containing many food granules, is large, being in diameter one fourth to one fifth of the whole organism. There is a large conspicuous karyosome which has a diameter of one third to one half of the nucleus.

The cysts are uninucleate, frequently irregular in outline, measuring 7–15 μ in diameter. There is a distinct cyst wall, and inside the cyst is a rounded

refractile body with a number of small *volutin* granules. There is usually a large and dense glycogen mass which shows up clearly in iodine solution, and sometimes even two or three separated masses may be observed within the same cyst.

The cyst nucleus, eccentrically placed, is comparatively large, 2–3 μ in diameter, whilst the karyosome, which is centrally placed in the nuclei of the precystic stage, gradually passes, during encystment, to the periphery, showing up as a large compact mass in close contact with the nuclear membrane.

It is remarkable that very large numbers of cysts may be present in the faeces without any evidence of free forms. The mature uninucleate cysts, save for the disappearance of the contained glycogen, do not undergo any further changes outside the human body.

It is estimated that *I. bütschlii* occurs in 5 per cent. of human faeces, most commonly in the tropics, and is found, not infrequently, in association with *E. histolytica*. Both the active forms as well as the cysts are amenable to emetine and emetine bismuthous iodide. This amoeba has been cultivated on egg medium and Locke's solution.

Pathogenicity.—A unique generalized amoebiasis due to *Iodamoeba bütschlii* in a Japanese prisoner of war has been described by Derrick (1948). This differed from any known infection of *E. histolytica* by the extent and bizarre nature of the lesions. These were—ulceration of the stomach, small intestine and colon. Metastatic foci were present in the brain, both lungs, gastric and mesenteric lymph glands, but not in the liver. In most of the lesions the amoebæ occurred in enormous numbers. In all tissues they had the same morphology and varied from 3 μ to 12 by 9 μ , on an average of that of a leucocyte in sections. It is conceivable that a set of circumstances arose when the host's resistance was much reduced which caused the amoebæ to invade the tissues—that there was a primary infection of the intestinal tract from which the amoebæ spread to other organs. The invasion of vessels, arterioles, venules and lymphatics readily explains the widespread metastases. It is suggested that primarily there was a heavy infection of the faeces with *I. bütschlii*.

Dientamoeba fragilis (Jepps and Dobell, 1918) (Fig. 283)

Genus: *Dientamoeba*.

This is a small species which may measure 3.5–12 μ , but its usual size is 8–9 μ ; it inhabits the large intestine of man and has also been found in monkeys (macaques in the Philippines).



Fig. 283.—*Dientamoeba fragilis*, uninucleate and binucleate forms.
× 2,500. (After Dobell.)

It is very actively motile, throwing out pseudopodia which are lobed and indented. Each amoeba is typically binucleate. The spherical *nucleus*, measuring 0.8–2.3 μ , contains six chromatin granules. The two nuclei are connected by a thread (*centrodesome*). In fresh preparations the amoeba rapidly degenerates and vacuoles form. It lives exclusively on bacteria and small micro-organisms, and is apparently amenable to emetine. No cystic stage is known.

Dobell has brought forward evidence that this amoeba is closely related to

the flagellate *Histomonas meleagridis* (the parasite of "blackhead of turkeys") which normally lives as a flagellate in the cæcum, but can invade the liver, where it assumes the amoeboid form.

Burrows and Swerdlow (1956) have recorded an abnormally high association between the incidence of *D. fragilis* and that of *Enterobius vermicularis*. Of 22 appendices harbouring *D. fragilis*, 12 were also infected with the pinworm. The association is supported to some extent by the supposed passage of *Histomonas meleagridis* of turkeys through the nematode—*Heterakis*.

Parasitism.—Most human amœbæ are liable to be parasitized by a fungus—*Sphærita*—consisting of a small spherical mass of coccus-like bodies, which are refractile and occur within vacuoles of the cytoplasm.

INTESTINAL FLAGELLATES

Order: Polymastigida.

Family: Tetramitidæ.

Genus: *Enteromonas*.

Enteromonas hominis (Fonseca, 1915) (Fig. 284, J-L)

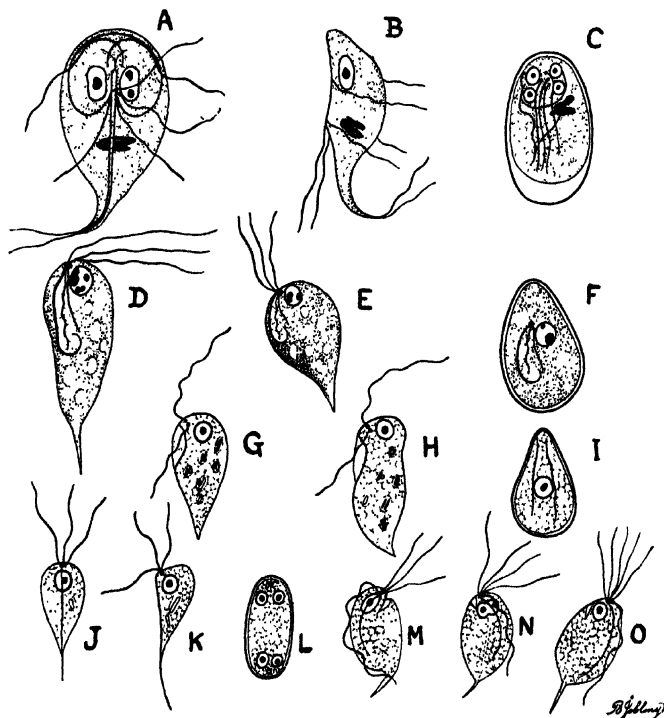


Fig. 284.—The flagellates of the human intestine. ($\times 2,000$). (After Wenyon.)

A-C, *Giardia intestinalis*, free and encysted forms; D-F, *Chilomastix mesnili*, free and encysted forms; G-I, *Eubadomonas intestinalis*, free and encysted forms; J-L, *Tricomonas intestinalis*, free and encysted forms; M-O, *Trichomonas hominis*, forms with three, four and five flagella.

Synonym.—*Tricercomonas intestinalis* (Wenyon and O'Connor, 1917).

This is a minute but very active pyriform flagellate, measuring 4–10 μ by 3–8 μ . The posterior end is attenuated to a fine point.

The *nucleus* is single and vesicular, and three flagella of equal length arise from a blepharoplast. A fourth flagellum runs down the margin of the body to the posterior extremity and ends in a terminal lash. The combined movements of all these produce a sort of "hovering effect" when in full action.

The *cysts* are small, oval, with a distinct cyst wall, resemble fungus spores, and contain iodophilic refractile bodies. This flagellate can be cultivated with comparative ease on Locke egg-medium. There is no evidence of pathogenicity.

Family: Bodonidæ. Genus: *Embadomonas*.

Embadomonas intestinalis (Wenyon and O'Connor, 1917) (Fig. 284, G-I).

A small but active flagellate, oval, 4–9 μ by 3–4 μ , which inhabits the intestinal tract. There are two flagella: the anterior longer and thinner; the posterior projecting from a laterally-situated mouth (cytostome), at the anterior extremity, supported by a ridge. The flagella act independently and thereby impart a peculiar jerky movement to the organism. The general shape is ovoid, with blunt anterior and pointed posterior extremities. The cytoplasm is vacuolated, containing ingested bacilli.

Cysts are pear-shaped, 4·5–6 μ in length, and appear structureless in the unstained state, but in iodine solution the *nucleus* can be discerned. This flagellate has been cultivated on egg medium. As in other members of this group, there is no evidence of pathogenicity.

Family: Chilomastigida.

Genus: *Chilomastix*.

Chilomastix mesnili (Wenyon, 1910)

Synonym—*Tetramitus mesnili* (Fig. 284, D-F).

This flagellate resembles *Trichomonas hominis* in general shape and size and occurs in the large intestine. There are three long flagella, but no undulating membrane or axostyle. There is a large mouth (cytostome), which occupies two-thirds of the body length, and contains a flagellum arising from a granule situated anteriorly to the spherical nucleus. The posterior extremity is attenuated. The cytoplasm contains numerous vacuoles and bacteria which form the main food supply. Division takes place by longitudinal fission. Individual organisms vary very much in length, but measure on an average 14 μ in length by 5–6 μ in breadth.

In freshly-passed fæces, *Chilomastix* moves with active, jerky movements which distinguish it from the more deliberate rotatory action of *Trichomonas*.

Cysts.—"Lemon-shaped" cysts appear in formed stools and are 7 to 10 μ in length; they contain a single nucleus and vestiges of a cytostome. In fresh preparations they have to be differentiated from yeasts.

Infections with this parasite are very persistent, but there is no evidence of pathogenicity.

C. mesnili has been cultured on artificial media.

Family: Trichomonadidæ. Genus: *Trichomonas*.

Trichomonas hominis (Davaine, 1860). (Fig. 284, M-O)

This is the most common intestinal flagellate of man, inhabiting the cæcum and large intestine, often in enormous numbers.

The body is pear-shaped, 10–15 μ in length by 7–10 μ in breadth. The spherical *nucleus* is at the anterior extremity and immediately in front of it are placed *blepharoplasts* from which three long flagella are directed forwards, whilst a fourth and stouter passes backwards to form the border of the undulating membrane, beyond which it is continued as a free flagellum. The cytostome is represented by a small aperture near the anterior end. A *stiffening rod*, arising from the blepharoplast, supports the undulating membrane. Running down the middle of the body is a second skeletal rod, or *axostyle*. The cytoplasm contains vacuoles with bacteria and food granules.

According to the number of flagella (3, 4, or 5), three varieties are recognized, although the triflagellate is the most common. Dobell thought that these varieties were merely strains of the same species. This flagellate progresses by lashing movements from the three anterior flagella, whilst the undulating membrane causes it to revolve on a longitudinal axis. The parasite is also capable of amoeboid movement, especially evident in degenerate individuals. Reproduction is by longitudinal fission, by duplication of the various parts. No cysts are known.

The abundance of *T. hominis* in diarrhoeic stools in the tropics has induced some observers to consider it pathogenic, and in one instance Wenyon found definite evidence of invasion of the intestinal mucosa by these organisms. Moreover, the closely allied *T. caviae* often causes ulceration of the large intestine in guinea-pigs.

On the whole, the pathogenicity of *T. hominis* in the intestinal tract of man is doubtful (see p. 503), and its presence in diarrhoeic stools may be due to liquid faeces which constitute a congenial medium for this flagellate.

T. hominis can be artificially cultured on blood agar with Locke's fluid for many generations, but subinoculations are necessary every few days, but now bacteria-free cultures can be obtained with antibiotics in egg-slants overlaid with bouillon serum and yeast extract.

A somewhat similar species, *T. elongata*, is found in the mouth cavity, as well as on the tonsillar surface. A third form, *T. vaginalis*, is present in the vaginal cavity of 10 per cent. of women. *T. vaginalis* can be grown easily in bacteria-free culture and its requirements are less exacting than those of *T. hominis*.

Most gynaecologists now regard *T. vaginalis* as a definite clinical pathogen, responsible for vaginitis, and the human analogue of *T. fetus*, which causes inflammation of the genitalia of cattle. The two species are physiologically different. On serological grounds it has now been shown that *T. hominis* and *T. vaginalis* are distinct species (Kot). *T. vaginalis* is sometimes found in the male urethra (Liston, 1940) and can invade the epithelium and prostate. Feo (1946) has brought forward evidence that the male is the most important transmitter of this infection. It flourishes mainly during the reproductive period, but not, as a rule, in young girls, or after the climacteric. It appears to multiply when the vaginal state is favourable, at pH 4, and a symbiotic association with a non-haemolytic streptococcus is suggested. The parasite disappears when the urine becomes alkaline. *T. vaginalis* is said to be considerably larger than *T. hominis* reaching 27 μ by 18 μ . Four anterior flagella are of equal length, a fifth flagellum on the margin of the relatively short undulating membrane protruding a considerable distance beyond the posterior tip of the organism. *T. tenax* (*Tetratrichomonas buccalis*) Dobell (1939), is probably a cosmopolitan parasite of man and has four anterior free flagella of equal length, a relatively short undulating membrane, a slender *axostyle* and a subspherical nucleus. On the average it is smaller than *T. hominis*. It inhabits the mouth, especially in diseased gums. It has been found in sputum from the lung and in pulmonary gangrene. It occurs in about 18 per cent. of individuals.

Family: Hexamitidæ. Genus: *Giardia*.

Giardia intestinalis (Lambl, 1859)

Synonyms.—*Giardia lamblia*; *Lamblia intestinalis* (Fig. 284, A-C.)

This remarkable parasite lives in the upper part of the small intestine, particularly the duodenum. In shape it resembles a half-pear, split longitudinally. It measures 12–18 μ in length. The ventral surface is furnished with a concave sucking disc with a raised ridge at the anterior end, whilst the posterior extremity tapers into a fine tail and terminates in two flagella. There are altogether four pairs of flagella on the body, arising from as many blepharoplasts; the posterior three arise from the margins of the *axostyles*. There are two of these stiff supporting structures which pass down the centre of the body. Two oval *nuclei* are situated within the sucking discs at the anterior end. The cytoplasm also contains a characteristically curved parabasal body in the lower half of the body. This flagellate swims rapidly, like a flat fish, swaying from side to side. *Giardia* reproduces itself by a complicated process of binary fission.

The *cysts*, which may occur in the fæces in enormous numbers, are characteristic structures. They are oval, measuring about 10.5 by 7.4 μ . The body of the flagellate becomes rounded, while the various inner structures (flagella, axostyle, etc.) become detached and cannot always be identified, except for the crescentic parabasal. There are at first two nuclei, which divide, giving rise to four in the mature cyst. When examined in iodine solution, the cysts stain faint yellowish-brown and the cytoplasmic contents shrink back from the thick wall.

Infections with giardia are very persistent, and it is found in the fæces for many years. Under certain conditions it may possibly assume a pathogenic rôle, and this fact has been more generally recognized since it has been found susceptible to atabrin. It has been found in the gall-bladder at operation and quite commonly in duodenal contents obtained by intubation (see p. 502). This parasite has not been cultured. Similar species of giardia are found in rats, mice, dogs and other animals.

Class: Ciliata Subphylum Ciliophora. Genus: *Balantidium*.

Balantidium coli (Malmsten, 1857)

This is a large protozoon belonging to the class ciliata. Oval in shape and of variable size, it is 30–200 μ in length by 40–60 μ in breadth. The average is 50–70 μ . Various races are recognized by the size. The body is clothed with a thick covering of cilia arranged in longitudinal rows. (Fig. 285.)

The *nucleus* is represented by a large kidney-shaped *macronucleus* with a small *miconucleus* closely approximated. The protoplasm contains two *contractile* and a number of *food vacuoles*. At the anterior end there is a *peristome*, leading into a mouth, or *cytostome*; posteriorly there is an anus, or *cytoppyge*. Nutrition is effected by ingestion of solid particles, leucocytes and red blood corpuscles.

Bal. coli reproduces asexually by transverse fission. Conjugation takes place by exchange of certain nuclear elements and, when once this has been effected, the conjugants once more separate.

The *cysts* (Fig. 285, 2) are ovoid, 45–60 μ in length, and are passed in the fæces. They contain the parasite which may be seen moving actively. The enclosed balantidium then loses its cilia, and sometimes two individuals are found in the same cyst. Transmission of infection takes place by means of cysts,

Bal. coli has been cultured in human serum diluted with saline. The presence of symbiotic bacteria is necessary, at 30–37° C, but frequent subinoculations have to be made.

Bal. coli not infrequently burrows into the intestinal mucosa and causes dysenteric symptoms—"balantidial dysentery," or "balantidiasis" (see p. 500). The balantidium is normally a parasite of the large intestine of the pig. Swine herds and pig-keepers are therefore particularly liable to infection. This parasite has been occasionally found in the mesenteric glands, as well as in the intestinal ulcers.

Bal. coli is a very active parasite and is frequently found in diarrhoeic as well as in bloody and mucous faeces. Balantidiasis in man has been recorded from France, Germany, England, the Philippines and Rodriguez. It has also been found in chimpanzees, monkeys, ruminants, guinea-pigs rats and other animals in captivity, often producing fatal results.

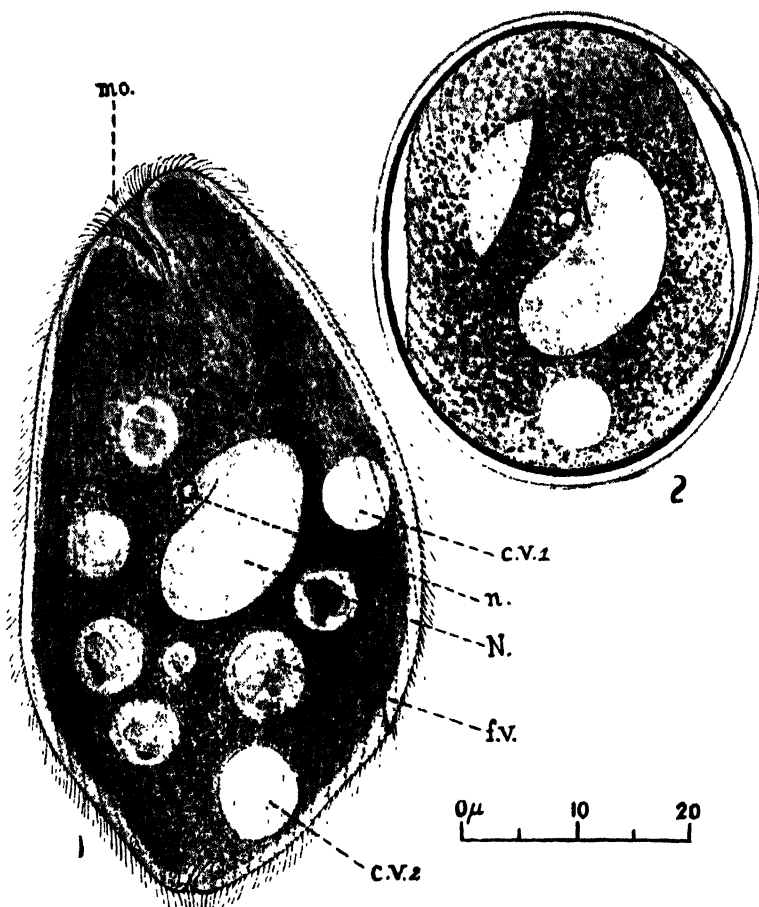


Fig. 285.—*Balantidium coli*. $\times 1,200$.

(After Dobell; by permission of Medical Research Council Report No. 51.)

- 1, Living individual; N., meganucleus; n, micronucleus; c.v.1, anterior contractile vacuole; c.v.2, posterior contractile vacuole; f.v., food vacuole; mo., mouth.
2, Encysted form, showing nuclei, posterior contractile vacuole, and remains of cilia.

II. Medical Helminthology

CLASS: TREMATODA OR FLUKES

PHYLUM PLATYHELMINTHES

SUPERFAMILY Fascioloidea

Genus: *Fasciola*

FASCIOLA HEPATICA (Linn., 1758).—Parasite of sheep, causing "liver rot." Also found in "Jack" and "Cotton-tail" rabbits in U.S.A. and rats in Old World.

Distribution.—World-wide.

Characters.—Pale-grey with dark borders, it measures 2.3 cm. by 8-13 mm.; large specimens in deer (7.5 cm.) are known as *F. gigantica*. The anterior extremity is narrow, containing the oral sucker; the ventral sucker is larger than the anterior and situated 3 mm. from the anterior extremity. Branched intestinal cæca with diverticula are present. The ovary is racemose, placed anterior to the testes in the posterior end of the body. The uterus is short and anterior to the ovary. An exsertile cirrus is present, and the genital pore is median.

The egg is operculated, 130-140 μ by 63-90 μ , ovoid, brown and bile-stained, and contains the ovum and yolk cells. A ciliated, eye-spotted miracidium develops in about three weeks, and enters freshwater snails: *Limnaea truncatula* (Europe), *L. pervia* (Japan), *L. vicetrix* (Cuba), *L. bulimoides* and *L. auricularia* (U.S.A.). Other snails are *Succinea*, *Fossaria*, *Praticolella* (a land-snail in Cuba), *Bulimus* and *Ampullaria*. In these it becomes a sporocyst, daughter sporocysts, rediæ (named after the Italian zoologist Redi) and cercariæ. Development takes two months. The cercaria is blunt-tailed and settles in grass or on bark, where it secretes mucus to form a cyst with two prominent suckers (metacercaria). Then it is eaten by the mammalian host. Metacercariæ excyst in the duodenum and migrate through the intestinal wall into the body cavity, then to the capsule of the liver to the biliary passages, where they grow to maturity.

Diagnosis.—This is effected by finding the characteristic eggs in the fæces or in the duodenal juice. The blood shows eosinophilia and there is sometimes an afebrile colic.

Pathogenesis and treatment.—This fluke has been found as an erratic infection in 150 human cases: probably it is commoner than is supposed in Cuba, Venezuela, Argentine, Hungary, Switzerland, Germany, Greece, Tunisia, China and England. Flukes have been reported from the bile-duct by the Editor and by Walton, and they have been found in the portal vein and in subcutaneous abscesses.

Five cases of human infection with *F. gigantica* in Hawaii have been reported. It is probably more frequent than generally recognized. Man is usually infected by eating watercress.

¹ The following is a key to the terminology of anatomy of trematodes, as illustrated in this and other figures: *a.s.*, anterior sucker; *m.*, mouth; *p.*, pharynx; *p.b.*, pharyngeal bulb; *ac.*, acetabulum or ventral sucker; *g.o.*, genital opening; *ut.*, uterus; *v.g.*, vitelline glands; *ov.*, ovary; *s.g.*, shell-gland; *va.*, vagina; *oo.*, oocyte; *ovd.*, oviduct; *v.s.*, vesicula seminalis; *r.s.*, receptaculum seminis; *t.*, testis; *v.d.*, vas deferens; *cs.*, cesophagus; *i.*, intestine; *i.c.*, branch intestine; *ex.p.*, excretory pore; *n.c.*, nerve cord; *l.c.*, Laurer's canal.

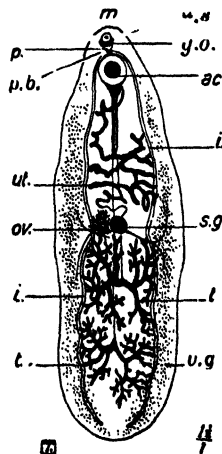


Fig. 286.¹—*Fasciolopsis buski*. (After Odhner.)

Usually they cause little disturbance save diarrhoea, but they may produce cirrhosis of the liver. Epileptiform fits have been described in Lebanon, and also a buccopharyngeal infection known as "halzoun." In some instances there is cachexia and severe anæmia with eosinophilia. Emetine is said to be efficacious, 12-12 gr. being given in separate courses; so also are massive doses of magnesium sulphate with intravenous stibosan or glucantime. Mohr argues that the febrile eosinophilic syndrome produced by the fluke is easily identified by irregular septic temperature, high eosinophilic leucocytosis, and enlargement of liver and spleen.

Genus: *Fasciolopsis*.

FASCIOLOPSIS BUSKI (Lankester, 1857) (Odhner, 1902). (Fig. 287.)

A parasite of the pig which constitutes a reservoir for man

Distribution.—China, especially; India (Assam), Straits Settlements, Sumatra, Borneo and Siam. In China 5 per cent., and in Kamarup District, Assam, 50 per cent. of the population are infected. Pigs and dogs are also infected. It is estimated that there are 10 million human infections in E. Asia.

Characters.—*F. buski* inhabits the small intestine, rarely the stomach; only a small number of those infected show symptoms. This is the largest human trematode, measuring 3 cm. by 12 mm., and 2 mm. thick. It is flesh-coloured, elongated and oval, with transverse rows of spines, especially numerous near the ventral sucker. The oral sucker is subterminal; but ventral in position and is only quarter the size of the ventral which is placed close to the oral, and prolonged into the cavity dorsally and backwards, a feature peculiar to this species. (For details of the anatomy see Fig. 286). The intestinal cæca are simple, with two characteristic curves towards the midline. The genital pore is median, placed anterior to the ventral sucker. Branched testes are found in the posterior half of the body; there is a branched ovary and a fine, tortuous, Laurer's canal.



Segmentina hemisphaerula

Gyraulus convexiusculus

Hippeutis cantori

Fig. 287.—Molluscan Hosts of *Fasciolopsis buski*. (C. J. Hackett.)

Development in the freshwater snail resembles that of *F. hepatica* (Nagakawa, 1920).

The egg (Pl. XXVII, 1) is operculated, and yellow, measuring 130-140 μ by 80-85 μ . Eggs are found in large numbers in the faeces, the egg capacity of each fluke being about 25,000 per day. In water, after three to seven weeks, they hatch a ciliated miracidium which develops in freshwater snails—*Segmentina hemisphaerula* (China, Formosa, Japan), *Segmentina trochoideus* (Assam), *Hippeutis cantori* (China) and *Gyraulus convexiusculus* (*saigonensis*) (Formosa, Japan, Indo-China, Philippines, Indonesia, India). A sporocyst is formed in three days, followed by the rediae and daughter rediae, which eventually produce cercariae (the whole cycle takes two months) (Fig. 287).

The cercariae, resembling those of *F. hepatica*, are oval, short-lived, lophocercous and measure 0.7 mm.; they have a well-developed digestive tract with a muscular bladder and collecting tubules. They encyst, as metacercariae, on fresh-water plants, especially the outer cuticle of the water-calthrop (ling), *Trapa* (*Salvinia*

natans in China; *T. bicornis* in India; *T. bispinosa* in Formosa. As many as twenty encysted metacercariæ may be found on a single leaf. In S. China the most important is the water-chestnut, *Eliocharis tuberosa*, also in *Zigania aquatica*, the water bamboo (Chekiang and Canton), *Eichhornia crassipes*, the water hyacinth (Formosa). The outer layers of the plants are torn off by the teeth. All the plants are grown in ponds in China, and fertilized by human faeces, thus affording an opportunity for infection; *F. buski* is therefore limited in distribution to that of these plants. The cysts, when taken into the mouth, pass through the stomach, excyst in the duodenum, and become attached to the intestinal wall.

Pathogenesis and treatment.—Often as many as 1,000–2,000 flukes are found in the small intestine, where they cause alternate diarrhoea and constipation, with offensive pale-yellow faeces and sometimes acute ileus. There is cedema of the face and also of the abdominal wall, genitalia and legs, and sometimes ascites. The pain may simulate duodenal ulcer. Death occasionally occurs from exhaustion.

Treatment.— β naphthol, ol. eucalypti, tetrachlorethylene and hexyl-resorcinol are all useful. For a child under seven 0.4 grm., and from 13 years upwards 1 grm. of the latter may be given.

SUPERFAMILY: OPISTHORCHIOIDEA.

Genus: *Clonorchis*.

CLONORCHIS SINENSIS (Cobbold, 1875) (Looss, 1907). (Fig. 288.)

Synonym-opisthorchis sinensis

Distribution.—Far East, especially China (Kwangtung Province in S. China and Indo-China).

Characters.—This is a common parasite of man and also of the biliary passages of the dog, cat, pig, rat, mouse, camel and badger. It is found rarely in the gall-bladder of man, but often in the bile-ducts, pancreas, pancreatic ducts and

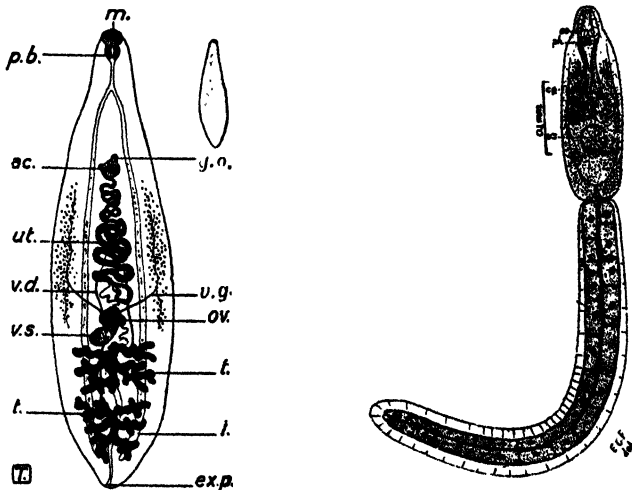


Fig. 288.—(1) *Clonorchis sinensis*, A, magnified; B, natural size. (Partly after Looss.) (For lettering, see p. 941, footnote.)

(2) Cercaria of *Clonorchis sinensis*. (After Faust and Khaw. By permission of "The American Journal of Hygiene.")

OS=oral sucker. PH=pharynx. OG=oesophageal gland. VS=ventral sucker.

duodenum. It is spatulate, tapering anteriorly, reddish, semi-transparent, and measures 10-25 mm. by 2-5 mm. The cuticle is smooth; the oral sucker is larger than the ventral; the intestinal cæca are simple.

The genital pore is median and placed anterior to the ventral sucker. The testes are branched, and situated posteriorly one behind the other. The ovary is trilobate, with coils anterior to the genital glands. Vitelline glands are moderately developed in the mid-third of the body. Cross fertilization occurs; the spermatozoa develop before the ova; the sperms enter the female genital pore, pass into the immature uterus and thence to the *spermatheca* (Fig. 288, *v.s.*), where they are stored; the ova are fertilized in the *spermatheca* and then pass on,

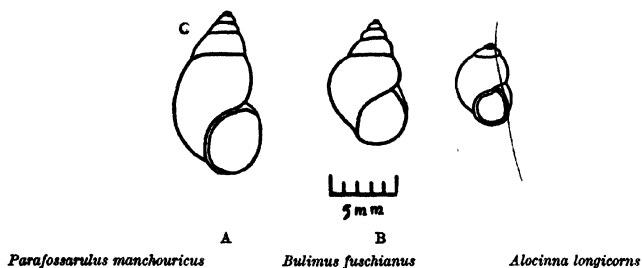


Fig. 289.—Molluscan Hosts of *Clonorchis sinensis*. (C. J. Hackett.)

The egg measures 20-30 μ by 15-17 μ (Plate XXVII, 5); it is operculated, yellow-brown, and one of smallest trematode eggs found in man, and is fully embryonated when discharged. It resembles an electric light bulb, with the knob at the bottom. It withstands desiccation but not decomposition. It can remain viable in water for five weeks, and is ingested by the snail before the escape of the miracidium, which has a life-span of 20 minutes (Vogel). Development continues in *Bulimus* (*Parafossarulus*) *striatula* (Japan, Korea and Formosa), *B. fuschianus*, *B. longicornis* (China) (Fig. 289) and in *Melania cancellata*. The miracidium pierces the œsophagus of the mollusc, casts its cilia and soon becomes a sporocyst; later, the elongated rediæ grow within the sporocysts and burst into the peri-œsophageal sinus and move tailwards into the liver; the whole process taking three to four weeks.

The cercariæ (Fig. 288, 2), 450-550 \times 100-120 μ , escape from the rediæ from the birthpore; they have two pigmented eyespots, a lophocercous blunt-ending tail, and burst through the space between the upper body surface and the shell, emerging into water. Within 24-48 hours they encyst, as *metacercariæ*, in the muscles and under-scales of fresh-water fish of genera *Cyprinidæ* and *Anabantidæ* (of which 34 species are susceptible). Cercarial glands excrete a histolytic substance which dissolves the skin of the fish, thus admitting percolating water. The *metacercariæ* secrete a viscous fluid which forms an inner true cyst, which in turn is encapsuled by a fibrous layer formed by the tissues of the fish. These are eaten half-raw, or pickled in *soy* sauce, by the Chinese. The *adolescercaria*, the fully-developed cyst, possesses a capsule protective against the gastric juice. In some species of fish—*Carassius auratus* and *Eleotris swinhonis*—the parasite is found under the scales; in others it is in the flesh, so that domestic animals which eat the offal may become heavily infected while man escapes. The cysts withstand a temperature of 50-70° C. for 15 minutes. The cyst wall is digested by the succus entericus in the duodenum near the papilla of Vater, and the *adolescercariæ* escape and attach themselves to the mucosa. The young

distomes at first have spines but these are soon lost. They attain maturity in 26 days. Attracted by positive chemotaxis, a small proportion of them reach the bile ducts, but 95 per cent. are digested and destroyed. The size of the resulting fluke is determined by the calibre of the bile-duct. Egg production is very large; in the cat 2,400 eggs are produced daily; but fewer in dogs. As many as 21,000 adults are found at autopsy (Sambuc and Beaujean). Life-span is 12 years. Adult men are more infected than women.

The following is a complete list of the molluscs and fishes which may be intermediaries:—

MOLLUSCA

Fossarulus stachei, *F. loczy*, *F. sinensis*, *Parafossarulus subangulatus*, *P. manchouricus* (Striatulus), *P. woodi*, *Pseudovivipara hypocrites*, *Hydrobiodes dautzenbergi*, *H. nassa* *Bulimus* (*Bithynia*) *striatula*, *B. longicornis* (*Alocinna longicornis*), *B. chaperi*, *B. moreletiana*, *B. poeteli*, *B. misella*, *B. umbilicaris*, *B. morleti*, *B. goniomphalos*, *B. thalkeana*, *B. robusta*, *B. minor*, *B. truncata*, *B. dautzenbergiana*, *B. siamensis*, *B. funiculata*, *Bulimus fuschianus*, *B. delavayana*, *B. toucheana*, *B. levis*, *Melania hainanensis*, *M. cancellata*, *M. hongkongiensis*, *M. tuberculata*, *M. variabilis*, *Vivipara polyzonata*, *V. quadrata* and *Hua* (*Namrutua*) *ningpoensis*. (Walker, Miyayana and Gaillard.)

The most important snail hosts are:—

<i>P. manchouricus</i>	China, Formosa, Indo- China, Korea, Japan.
<i>B. fuschianus</i>	S. China.
<i>Alocinna longicornis</i>	China.
<i>Hua ningpoensis</i>	China.

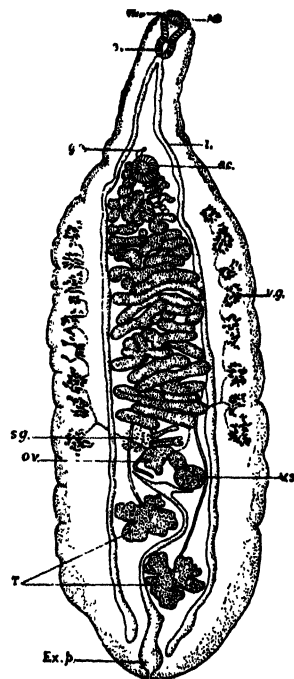


Fig. 290.—*Opisthorchis felinus*. $\times 9$. (After Barker in "Arch. de Parasitologie.") (For lettering see footnote on p. 943.)

PISCES

Hemiculter kneri, *H. clupeioides*, *Acanthorhodeus atranalis*, *A. gracilis*, *Carassius auratus*, *Pseudogobio rivularis*, *P. sinensis*, *Pseudorasbora parva*, *P. fowleri*, *Eleotris swinhonis*, *E. potamophila*, *Paracheilognathus rhombea*, *Rhodeus sinensis*, *R. notatus*, *Culter aburnus*, *Sacrocheilichthys nigripinnis*, *S. sinensis*, *S. morii*, *S. variegatus*, *Macropodus opercularis*, *Biwia zezera*, *Xenocyprys davidi*, *Pseudoperilampus typus*, *Abbotina psegma*, *Leucogobio guentheri*, *L. striatus*, *L. coreanus*, *L. mayeda*, *L. herzensteini*, *Ctenopharyngodon idellus*, *Acheilognathus lanceolata*, *A. limbata*, *A. cyanostigma*, *Labeo jordani*, *Hypothalmichthys nobilis*, *Mylopharyngodon aethiops*.

The most important cyprinoid fish are:—*Mylopharyngodon aethiops*, *Ctenopharyngodon idellus* (Canton) and *Culter aburnus* (Peking).

For pathogenesis, see p. 783.

C. sinensis is often associated with carcinomatous changes in the liver and pancreas.

Genus: *Opisthorchis*.

OPISTHORCHIS FELINEUS (Rivolta, 1884) (Blanchard, 1895). (Fig. 290)

Distribution.—It is common in man in East Prussia (Kurisches Haff), Siberia, Annam and the Philippines; and in the dog, cat, glutton and pig.

Characters.—It inhabits the liver, pancreas, bile ducts and lungs (in Russia). It is lanceolate, and measures 8–11 mm. by 1.5–2 mm. The cuticle is smooth, the suckers equal in size and separated by 2 mm. (Fig. 290). The egg measures $30\ \mu$ by $12\ \mu$ (Pl. XXVII, 4) and is yellowish-brown with an operculum. At the posterior end there is a minute tubercular thickening.



Fig. 291.—*Bulimus tentaculatus*. Molluscan Host of *Opisthorchis felineus*. (C. J. Hackett.)

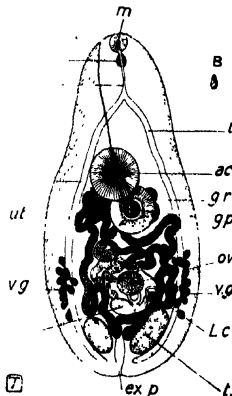


Fig. 292.—*Heterophyes heterophyes*.

A, Greatly magnified; B, natural size. (For lettering, see p. 941, footnote.)

Development (Vogel).—The snail is the intermediary host, usually *Bulimus* (*Bythinia*) *tentaculatus* and *B. leachi* (Fig. 291). The miracidium is fully formed in the egg and hatches in the snail, forming a sporocyst in the intestine measuring 1.2–1.85 mm. Rediae are formed in one month, and then cercariae which mature in two months.

Cercariae, $430\text{--}670 \times 40\text{--}50\ \mu$, leave the snail by daylight. They are shaped like a tobacco-pipe, with tail membrane; they are phototactic, and stimulated by agitation. The secondary intermediary hosts are fish—the tench (*Tinca tinca*) and the chub (*Idus melanotus*). The cercariae penetrate in 15 minutes, and grow to three or four times their original size, forming *metacercariae*, $220 \times 160\ \mu$. When ingested by man, they pass through the stomach, are freed by the succus entericus, attracted by the bile and travel up the bile-duct in five hours. Infection is therefore contracted by eating raw fish. The entire life-cycle requires a minimum of four months. This fluke is not specially pathogenic, although 200 or more have been found in the body at autopsies. Another variant (?) of this fluke, Gomez and Rodriguez (1949), has been described as a parasite of man in Ecuador; 32 per cent. of 214 persons in a village and 3 per cent. of dogs were found infected.

Other species of importance are *O. noverca* and *O. viverrini* (India and Siam), of which the normal hosts are the dog and civet cat respectively. This parasite has now become a "major" clinical problem in Siam where it is associated with carcinoma of the liver (Viraniwatti and Mettigawongse). The action of chloroquine upon this fluke has aroused some interest.

Genus: *Heterophyes*.

HETEROPHYES HETEROPHYES (Siebold, 1852).

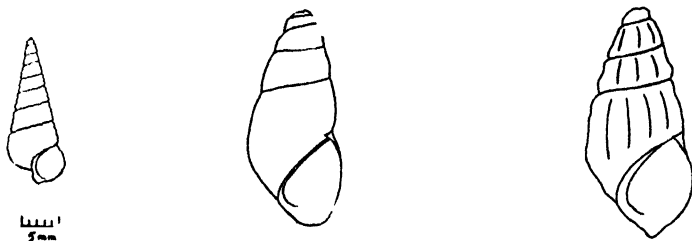
(Fig. 292)

Distribution.—Egypt, China, Japan (cases reported from Missolonghi in Greece).

Characters.—It inhabits the small intestine of man in large numbers and also that of the rat, fox, dog, wolf, jackal and cat; also in the Black Kite (*Milvus migrans aegyptius*) and a bat (*Rhinolophus divosus acrotis*) in the Yemen. It imparts a coffee-grounds appearance to the intestinal wall. It is pyriform, grey and very small, measuring 1·7 mm. by 0·3–0·7 mm. The uterus forms a brown patch in the centre. The oral sucker is subterminal and the ventral sucker is three times the size of the oral. The cuticle is thickly set with quadrate scales measuring $5\mu \times 4\mu$. There is a short prepharynx and long oesophagus. The intestinal caeca extend to the posterior extremity, converging close to the excretory vesicle. The vitelline glands are posterior, situated in two clumps; the genital pore is postero-lateral, in the vicinity of the ventral sucker, and consists of a muscular ring armed with 70 chitinous cuticular teeth. The testes are oval and posterior, the ovary globular and median. There is a *receptaculum seminis* as large as the ovary; uterine coils are not numerous. Seminal vesicle and Laurer's canal are present.

The egg measures 20–30 μ by 15–17 μ (P. XXVII, 3), being the same size as that of *C. sinensis*. Its greatest breadth is across the centre. There is no special ring to the operculum, which is light-brown and contains a ciliated miracidium when deposited. It hatches after ingestion by the appropriate snail.

Life-history.—*H. heterophyes* develops in brackish-water snails: *Melania tuberculata*, *Cleopatra bulimoides*; and in L. Manzala (Egypt), in a conical snail, *Pironella conica* (Khalil) (Fig. 293, A). The cercaria, resembling that of *M. yokogawai*, is oculate and lophocercous (membranous-tailed); it was formerly known as *C. pleurolophocerca* (Sonsino). The second intermediary is a fish—the mullet (*Mugil cephalus*) and minnow (*Gambusia affinis*); in Japan a species of *Acanthogobius*. There also a brackish fresh-water snail, *Tymphonotomus micropterus*; (also known as *Cerithidea cingulata microptera*) which is the molluscan host.



A.—*Pironella conica*

B.—*Semisulcospira libertina*. Snail Host of *Metagonimus yokogawai*

C.—*Hua amurensis*. Snail Host of *Paragonimus westermani*

Fig. 293.—A Molluscan host of *Heterophyes heterophyes* and others B and C. (C. J. Hackett.)

Pathogenesis and treatment.—This fluke occurs in enormous numbers, attached to the mucosa of the small intestine; it may give rise to diarrhoea. In Manila, heterophyes eggs are found in the walls of the intestines and in the myocardium and are said to produce symptoms resembling cardiac beriberi. Africa has recognized two other human species—*H. brevicerca* and *H. taihoku*. In Japan, in the vicinity of Kobe, *H. katuradai*, a closely-related stouter species,

which has a relatively enormous acetabulum, is found. The eggs are smaller, measuring $25-26\ \mu$ by $14-15\ \mu$. The flukes are removed by tetrachlorethylene, oleoresin of aspidium and piperazine adipate and citrate, 0.9-4.5 gm. (Nagaty), (see p. 872).

Genus: *Metagonimus*.

METAGONIMUS YOKOGAWAI (Katsurada, 1912). (Fig. 294)

Distribution.—Korea, Formosa, Japan and Balkan States, very common in Far East.

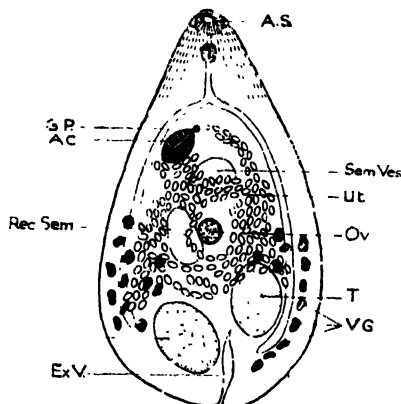


Fig. 294.—*Metagonimus yokogawai*. $\times 45$. (Partly after Leiper.)

Sem. Ves., seminal vesicle; Rec. Sem., Receptaculum seminis; G.P., genital pore. (For other lettering, see p. 941, footnote.)

Characters.—This is found in the small intestine of man, higher up than *H. heterophyes*, and also in the cat, dog, pig and pelican. It is the smallest fluke parasitic in man, measuring 1.1 mm. by 0.42-0.7 mm. The cuticle is covered with small spine; the ventral sucker is deflected to the right with its long axis in the diagonal plane. There is a genital pore in front; the ovoid testes are posterior; the ovary and receptaculum seminis are situated medianly in front of the testes. The yolk glands are found in clumps in the posterior third. The uterus lies between the testes and the ventral sucker, and the seminal vesicle in front of the ovary (Fig. 294).

Egg.—This measures 27 by 16 μ and resembles that of *C. sinensis*, but is more regularly ovoid (P. XXVII, 6).

The first intermediaries are molluscs—*Melania* (*Semisulcospira*) *libertina* (Fig. 293B). *M. ebenina* and *M. obliquegranulosa* (50 per cent. of which are infected). Sporocysts, rediae and cercariae are formed; the last has an anterior end provided with armament. The tail is long and lophocercous, with lateral flutings, and is discarded on entering the fish—*Plecoglossus altivelis*, Japan and U.S.S.R. The metacercariae, 150 by 100 μ , encyst under the scales; the infected fish is eaten raw by the Japanese.

Pathogenesis.—*M. yokogawai* causes a catarrhal condition of the intestinal tract and slight diarrhoea, but is easily removed by tetrachlorethylene.

Superfamily: Troglotrematoidea.

Genus: *Paragonimus*.

PARAGONIMUS RINGERI (Cobbold, 1880)—“Lung fluke”, and allied species *P. westermanii*, *P. compactus* and *Poikilorchis congolensis*. (Fig. 295).

Distribution.—Mostly Japan, Korea, Philippines, in Venezuela (Iturbe), Ecuador, Colombia, Peru, China, Manchuria, Indo-China, Siam, Malay States (Singapore), Malabar, Madras, Assam and French W. Africa, Nigeria, Belgian Congo and Somalia, S. Cameroons (2-5 per cent.). It is found in man, dog, wolf, leopard and cat, especially in the lungs.

Characters.—*P. ringeri* measures 8-20 mm. \times 5-9 mm. and is oval (almost round in section), reddish-brown and translucent. The anterior extremity is rounded. The oral sucker is subterminal; the ventral sucker larger and placed anterior to the centre of the body. The pharynx and oesophagus are short, and

the bifurcation of the intestine is anterior to the ventral sucker (Fig. 295). The intestinal cæca run a zigzag course; the common genital pore lies close to the posterior margin of the ventral sucker. The body is bisected by a large excretory vesicle. The testes are tubular and racemose; the branched ovary may be either to the right or the left of the midline and posterior to the ventral sucker. The uterus is short, sac-like and lies opposite the ovary. The vitellaria are well developed, extending through the whole body. Laurer's canal and shell-gland are present. The cuticle is studded with wedge-shaped spines and constitutes a reliable feature to differentiate closely-allied species. In *P. westermanii* they are arranged singly, and in *P. compactus* they are in clumps, fewer and pointed.

The egg is brown and operculated, measuring $90\ \mu$ by $55\ \mu$. It shows a thickening at the pole opposite the operculum (*P.* XXVII, 2). That of *P. westermanii* measures $85\ \mu$ by $55\ \mu$ and has the thickening at the posterior end, not so marked. The egg of *P. compactus* is smaller, $75\ \mu$ by $48\ \mu$.

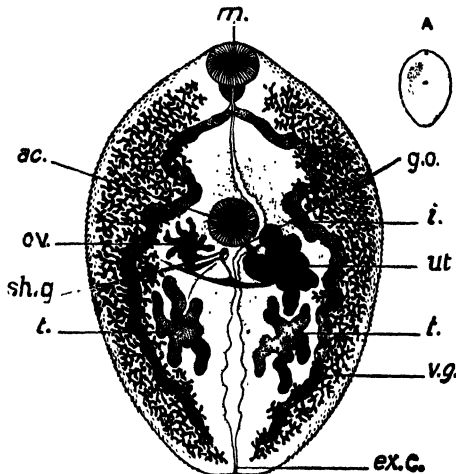


Fig. 295.—*Paragonimus (westermanii) ringeri*. (Partly after Looss.)

A, Nat. size. (For lettering, see p. 941, footnote.)

Geographical distribution.—This differs with the species. *P. ringeri* is found in Japan, Korea, Indo-China, Siam and the Philippines; *P. compactus* and *P. westermanii* in India, Malaya and North Africa, *Poikilorchis congolensis* found in Southern Nigeria, British Cameroons and the Belgian Congo. A fifth species is *P. kellicotti*, from the pig, dog and cat in North and South America, and the tiger in Malaya; it has once been recorded in man.

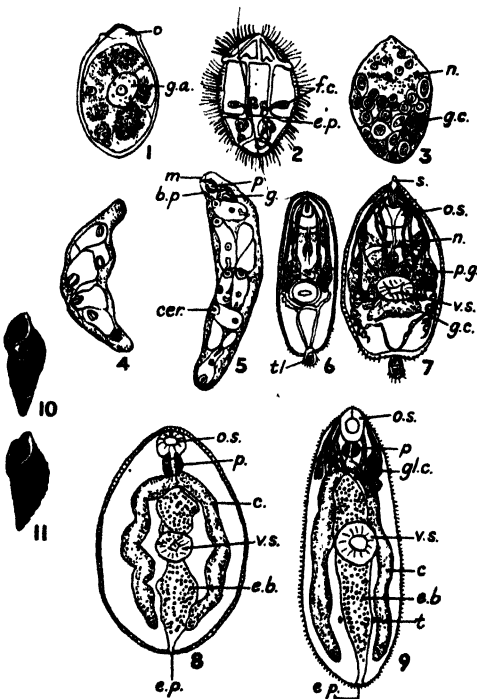
P. congolensis, Fain and Vandepitte (1957), discovered in retro-auricular cysts in Congo natives (Kasai). Eggs in pus, smaller than those of *P. ringeri*, $40\text{--}70\ \mu$, were found in sputum in S. Cameroons.

Life-history.—This is complicated. (Fig. 296.) The eggs are first voided into cystic pockets in the lungs and then escape into water in the sputum and also in faeces from swallowed sputum. A ciliated miracidium hatches in sixteen days to seven weeks and has distinctive characters. There is a ciliated covering in four rows at the anterior cone. The excretory pore forms a rosette. The lung fluke can remain viable in the human body for 20 years. It enters snails of the

genus *Melania* (or *Thiara*, *Semisulcospira*, *Brolia*). *M. tuberculata* (Japan, China), *M. libertina* (Japan, China), *M. ebenina* (Korea), *M. obliquegranulosa* (Formosa), a synonym for this species in America is *Thiara* (*Tarelia*) *granifera*, and *M. paucicincta*, *Hua amurensis* (Fig. 293), also known as *Brolia gottschei*, *M. nodiperda* (Korea), all these are common species living in fast flowing streams in S.E. Asia, Indonesia, Formosa, and W. Pacific Islands. In China, sometimes it develops in *Syncera lutea*; in Venezuela (*P. kellicotti*)—*Ampullaria luteosoma*. *Pomatiopsis lapidaria* (N. America). It develops in about 60 days into sporocyst and rediae, each containing 20 cercariae; the latter, ellipsoid and microcercous, have a short knob-like tail and measure $200\ \mu$ by $70\text{--}80\ \mu$ with an anterior stylet and body covered with spines. The cercariae bore into fresh-water crabs and

Fig. 296.—Life history of *Paragonimus westermani*. (After Belding and Cheng.) (1–9 $\times 15$.)

1. Egg showing yolk cells and germinal area.
 2. Miracidium with excretory system and flame cells.
 3. Miracidium with ganglionic mass and germ cells.
 4. Mature sporocyst in snail containing well-developed first generation rediae.
 5. Mature second generation rediae.
 - 6, 7. Stages of microcercous cercaria after emergence from snail.
 8. Metacercaria from the crab; cyst wall is not shown.
 9. Mature excysted metacercaria.
 10. *Melania libertina* } half
 11. *Melania obliquegranulosa* } natural size
- Key
 b.p. birth pore.
 c. caeca.
 cer. cercaria.
 e.b. excretory bladder.
 e.p. excretory pore.
 f.c. flame cell.
 g. gut.
 g.a. germinal area.
 g.c. genital cells.
 m. mouth.
 n. nervous system.
 o. operculum.
 o.s. oral sucker.
 p. pharynx.
 p.g. periacetabular glands.
 s. stylet.
 t. testes.
 tl. tail.
 v.s. ventral sucker.



become metacercariae in *Potamon obtusipes*, *P. rathbuni*, *P. dehaani* (Fig. 297) *Sesarma dehaani*, *S. sinensis*, *Eriocheir japonicus* (Fig. 298), Crayfish, *Astacus japonicus*; in Korea, *Eriocheir sinensis* and *A. similis*. In Venezuela the species is *Pseudothelphusa iturbei*; in the Philippines *P. mistis*. The cercariae perish in 24 hours if they fail to penetrate the appropriate crustacean host.

The crab *E. sinensis* has been introduced into North German rivers in the bilge water of ships from China; it has multiplied enormously, but *Paragonimus* has not spread, because *Melania* is not present.

In the crustacean (the second intermediary) the metacercariae encyst in the liver, muscles and gills. In Japan, crabs are eaten raw, but in Korea and Formosa they are not eaten; the supposition is that the crustacean phase is not always a biological necessity. In Venezuela the appropriate snails and crustacea are

present and 30 per cent. of dogs are infected, but man is not. When the metacercariæ enter the stomach of man, their cyst wall is digested and the *adolescercariæ* emerge, pass through the jejunum, traverse the abdominal cavity, penetrate the diaphragm, pleura and lungs, reach the bronchioles forming cystic cavities. (For Pathogenesis and Treatment, see p. 779.)

A trematode of less importance is *Echinostoma lindensis*. Of this, a few cases



Fig. 297.—*Polamon dehaani*. Half nat. size.

from Celebes (Brug, Tesch, Bonne and Sandground, 1938-40) are reported, with flukes, sometimes in large numbers, in the jejunum. Reservoir host is the field rat. It causes diarrhoea, abdominal pains and eosinophilia. Development. First intermediary: planorbid snails:—*Anisus sarasinorum* and *A. convexusculus*.

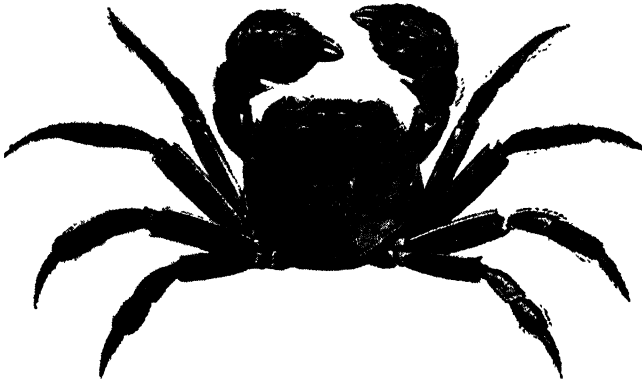


Fig. 298.—*Eriocheir japonicus*, ♂. Quarter nat. size.

Second intermediary (metacercariæ), in snails:—*Vivipara javanica rudipellis* and two species of mussel:—*Corbicula lindensis* and *C. subplanata*. All snails in Lake Lindoe, near heavily-infected village, were found to harbour large numbers of echinostome cercariæ, which have simple tails and a body resembling in miniature that of the adult worm. The eggs are straw-coloured, operculate and measure 83-116 μ by 58-69 μ . Immature when passed in the faeces, they mature in 6-15 days. Filix mas and tetrachlorethylene treatments are specific.

Superfamily: ECHINOSTOMATOIDEA.

Genus: *Echinostoma*.

E. ilocanum and the closely allied *E. malayanum* (larger) are found in Singapore

and Malaya. Natural host is the pig. The snail host is *Gyraulus prashadi*. Also *E. jassyens* in Rumania, *E. recurvatum* in Java and *E. sufrartylfex* in Assam—all removed by filix mas.

Superfamily: PLAGIORCHIOIDEA.

Genus: *Dicrocoelium*.

Dicrocoelium dendriticum SYN. *D. lanceatum*, of which the normal host is the sheep, is rarely found in man, in biliary tract in Germany, Czechoslovakia, Italy, France, Egypt, China. The eggs passed in faeces are fully embryonated, resist desiccation and do not hatch in water. They are ingested by land-snails—*Zebrina detrita*, *Hellicella candidula*, *H. itala*, *Torquilla frumentum*, *Cochlicella acita* and others.

Genus: *Plagiorchis*.

Plagiorchis javanensis. Sandground (1940) found this species in small intestine of Javanese, together with *E. ilocanum*. It is a small trematode belonging to group normally infecting birds, fish, amphibia and bats. Development takes place in a snail—*Stagnicola emarginata angulata*. Another species is *P. philippinensis*, recovered at autopsy in Manila from the small intestine of a native who had eaten grubs of certain insects.

Superfamily: SCHISTOMATOIDEA.

Genus: *Schistosoma*.

Distinctive characteristics.—These are unisexual (the sexes being separate) and inhabit the lumen of veins.

SCHISTOSOMA HÆMATOBIUM (Meckel, 1856). (Figs. 299A and 299B)

Synonym.—*Bilharzia hæmatobia* (Weinland, 1858).

Discovered in man by Bilharz in 1851, it was found in the sooty mangabey monkey (*Cercocebus fuliginosus*) in 1859 by Cobbold.

Distribution.—Africa, especially Cape Province; small foci in Portugal, Cyprus, Corsica, Palestine, Arabia, Madagascar, Réunion, Mauritius and Iraq; a new endemic focus in Ratnagiri, S. of Bombay. Also found for a short period in Perth, Western Australia, imported by returned soldiers from the South African War (1901).

Characters.—The male is 1.5 cm. by 1 mm., white and cylindroid, with oral, and more prominent, ventral suckers situated close together; the oral has a dorsal lip, longer than the ventral. Ventral infolding of the body forms *gynæcophoric canal*, which encloses the female. The outer surface, especially the dorsal, is beset with cuticular prominences (usually confined to the extremities of the worm), including delicate spines on suckers and larger tuberculations on the inner surface of the gynæcophoric canal. The ventral surface is beset with very fine spines. The male progresses along a vein carrying the female; the tuberculations aid progression against the blood-stream and along narrowing veins.

There are 4–5 testes which are round and placed posterior and dorsal to the ventral sucker (acetabulum). A similar number of *vasa efferentia* unite to form the *vesicula seminalis* at the genital pore which is placed median, posterior to the ventral sucker.

The female is darker, measuring 2 cm. by 0.25 mm.; her filiform middle portion is infolded in the gynæcophoric canal, her anterior portion being free. The body is smooth with papillæ on the posterior end and on the suckers. An elongated oval ovary is found in the posterior half, anterior to the intestinal cæca. The oviduct arises from the posterior portion of the ovary, passes forward, and is joined by the vitelline duct. Vitellaria (yolk glands) are seen in the posterior part. The shell gland opens into the oviduct, which passes forward to a straight uterus. The genital pore is median, posterior to the ventral sucker; the anterior portion

of the uterus contains several (20–30) terminal-spined eggs. The genital openings of both sexes face each other.

In both sexes the alimentary canal commences at the oral sucker, which is prehensile, and consists of an oesophagus, with two dilatations which bifurcate, in front of the ventral sucker to form two intestinal cæca uniting into a median trunk in the centre of the body.

The excretory system consists of two longitudinal canals opening posteriorly, dorsal to the excretory pore.

The nervous system has an oesophageal ganglion and commissure encircling the oesophagus, and two longitudinal nerve cords running to the posterior end of the body intercommunicating by lateral branches.

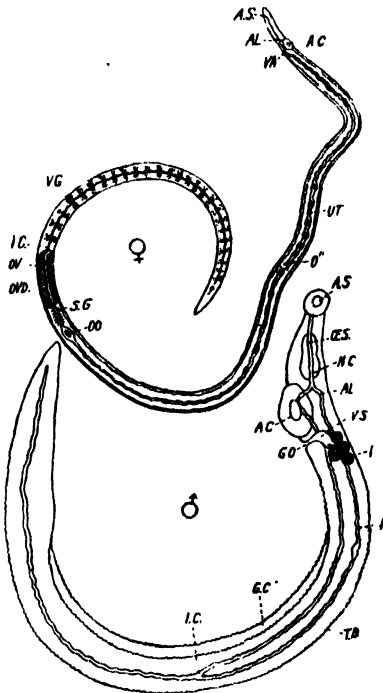


Fig. 299A.—*Schistosoma hæmatobium*. $\times 10$.

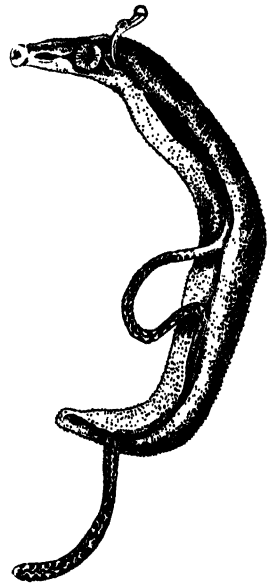


Fig. 299B.—*Schistosoma hæmatobium*. $\times 10$. (After Looss.)

A.C., Ventral sucker; AL., bifurcation of alimentary canal; A.S., anterior sucker; G.C., gynæcophoric canal; G.O., genital opening; L., intestine; I.C., union of intestinal cæca; N.C., nerve cord; O., terminal-spined ovum; G.S., oesophagus; O.O., ovotype; O.V., ovary; O.V.D., oviduct; S.G., shell-gland; T., testes; T.B., tuberculations; UT., uterus; V.A., vagina; V.G., vitelline glands; V.S., vesicula seminalis.

Habitat.—It lives in the venous system, the mesenteric, portal, vesico-prostatic, pelvic and uterine plexuses, the vesical veins, occasionally also in the vena cava and pulmonary veins. Sometimes 300 or more are present; they are more numerous still in experimentally-infected monkeys, being found specially in the submucosa of the bladder. They can be conveyed experimentally to rats, mice, guinea-pigs, hamsters, monkeys, hedgehogs and armadillos (Pinto). *S. hæmatobium* lives and ovulates for 26 and probably as long as 40 years and may produce carcinomatous changes in bladder. The sexes live apart while

young, but, when mature, the female enters the gynæcophoric canal of the male. Bisexual and hermaphrodite males, as in *S. spindale*, are sometimes met.

Monkeys, mice, hedgehogs, and especially hamsters can be infected with this parasite in the laboratory, but experimental animals are much more difficult to infect with *S. hæmatobium* than with *S. mansoni* and the former takes longer to mature (80–100 days) than the latter (50 days) (Watson, 1948).

The egg is oval, measuring $150\ \mu$ by $60\ \mu$, short, stout, and has a definite terminal spine (Pl. XXVII, 11). It contains the living, ciliated miracidium, the head of which lies towards the blunt end of the egg, but is active so that it can turn about.

When deposited in the tissues there is a thin and permeable clear space of dissolved cells in front of the egg, probably produced by a lytic substance secreted by the glands of the miracidium. The egg shell is permeable so that antimony can enter and kill the miracidium (Fig. 175, p. 699).

In freshly-passed urine the eggs appear brownish and contain active miracidia (Fig. 300) which develop early and are fully formed when they are deposited in the tissues. They escape by the transverse rupture of the shell, effected by osmosis in contact with water (dilution of urine with 10 parts of water), the shell being softened by a lytic ferment secreted by the miracidium. Temperature is important, as the eggs hatch more readily in warmth. The egg-shell enlarges before bursting. If the specific gravity of the urine is low, the eggs may hatch in urine within the bladder. The process is physical and will take place if the miracidium is previously killed by heat. The egg can remain alive in sterile urine, or moist faeces, for two or three weeks, but acid urine kills it. The miracidium is active and swims in water for 24 hours. It has an anterior papillary beak

but when swimming it changes shape and moves by means of cilia and muscular action. It has a primitive alimentary canal, two unicellular cephalic (salivary) glands, the ducts of which lead into the mouth, also germ cells, excretory tubules and four flame-cells. The nervous system is an oval irregular mass, in the centre. The cuticle is composed of polygonal epithelial cells; the body has three zones, united by six or seven longitudinal strands.

After escape of eggs from the tissues the paired worms travel to the narrowest point; the female then leaves the male and penetrates into the smallest venules, where she deposits her eggs, which are then clamped in position by spasm of the veins. The female retracts after deposition of the egg, so that the spine is driven into the wall of the vein and the egg escapes into the tissues. (Fig. 304.) This is not generally accepted by all observers. According to Koppisch the eggs are engulfed by endothelial cells and this facilitates their passage through the vessel walls.

The eggs of *S. hæmatobium* are often found in faeces (p. 697). Chesterman commonly found eggs in faeces (see *S. intercalatum*) in the Congo and Upper Egypt. Sometimes they are deposited in the lungs, brain and spinal cord. By rectal biopsy it can be ascertained that eggs of *S. hæmatobium* are present in the rectal mucosa in the great majority.

Life-history.—Miracidia penetrate the air sac, tentacles and other portions of the snail, boring in by their papilla. If there are many, the snail dies. They are attracted by several species of *Bulinus*. The miracidium casts its cilia and travels via the lymph spaces to the liver or digestive gland. Infection of snails

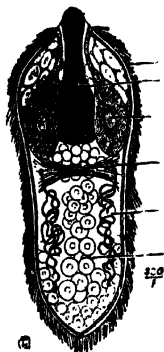


Fig. 300.—*S. hæmatobium* miracidium. (After Loosa.)

takes place in the warm season in Egypt, but not in the winter, and there is a seasonal variation in the number of snails. The two maximal periods in Egypt are May and December, with two marked reproductive periods—one in March and April—the other in October and November. During the Nile floods they die in large numbers, but reproductive activity stops temporarily during the winter closure of the Nile. On the return of the water into the canals the snails revive and commence laying eggs. The snail acquires immunity from slight infections. The liver of the snail is turgid, swollen, yellow or orange, and by its appearance infected molluscs may be recognized. The miracidium becomes an elongated, thin-walled sporocyst and subsequently daughter sporocysts permeate the gland. In about six weeks numerous bifid-tailed *cercariæ* appear within the sporocysts, and escape from it by a diurnal discharge from the pulmonary cavity of the snail, and are attracted by light. They cast off their tails on entering the skin of the host. Penetration is effected by the acid secretion of the glands, which cause a vesicular dermatitis. Most cercariæ die in transit, otherwise the infection would be colossal. For example, 30,000 may enter a mouse, but only 20 adults develop. The cercariæ adhere to the host by their ventral sucker and penetrate the mucous membrane of the mouth or œsophagus. Thus people can be infected by drinking, e.g., women and children in Egypt. In bathing, movement of the water attracts the cercariæ to hold on to the skin.

(For anatomy of cercaria, see p. 964.)

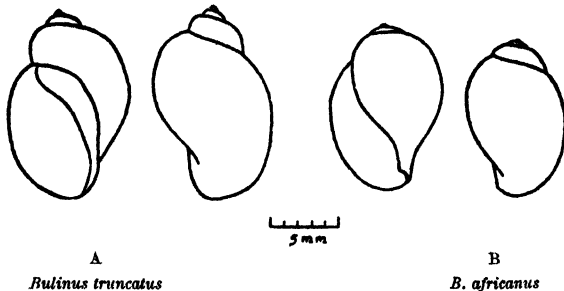


Fig. 301.—Molluscan hosts of *S. hæmatobium*. (C. J. Hackett.)

It is not true, as often asserted, that schistosome cercariæ, discharged from a single naturally infected snail, are of one sex. This statement is true only when the snail has been exposed to a single miracidium.

On entering the body of man the larvæ are known as metacercariæ, but within 24 hours they have entered the peripheral venules, through which they are transported to the right heart and to the pulmonary capillaries, squeezing through these to the pulmonary venules, they are carried passively through the mesenteric capillaries and enter the portal circulation. They are then known as *Schistosomulae*. They mature in the liver in six weeks and produce terminal-spined eggs. Infection is easily effected in the laboratory by inserting the tail of a mouse in water containing cercariæ. In man and in animals, infection of the portal veins causes a deposition of hæmatin in the interstitial cells.

Intermediary molluscan hosts: *B. abyssinicus* (Ethiopia and Somaliland), *Bulinus contortus*, *B. dybowskii* (Egypt and North Africa, Portugal, Southern Spain, Palestine, Mauritius, Syria, Iraq, Bombay, Persia, Cyprus).

B. contortus, *B. dybowskii*, *B. innesi* (N. Africa), *B. jousseaumei*. (Gambia and Palestine).

B. (Pyrophysa) forskalii. (Mauritius, Gambia, N. Nigeria and Kenya).

B. couboisi (L. Tanganyika, Belgian Congo).

B. (Physopsis) africanus (S. Africa and Cape).

B. (Physopsis) globosus (Central Africa and S. of N.12°).

B. (Physopsis) nasutus (Uganda, Tanganyika, Zanzibar.)

Biomphalaria (Planorbarius) metidjensis (Portugal, Morocco, Algiers).

In the Bombay focus the vector is still uncertain—*Paludomus obesi* var. *philippi* was first suspected; recently *Ferrissia tenuis*, an ancyloid snail. In the genus *Bulinus* the body of the snail contains red hæmoglobin. The shell is spiral, not operculated, and the opening is sinistral (Fig. 301). (The capacity of these snail hosts varies in different districts. Thus *Bulinus forskalii* cannot be infected in the Congo, but is efficient in Nigeria, Portuguese Guinea, Uganda, Kenya, Saudi Arabia, Egypt and Nyasaland. According to Anderson and Schwarz (1953) *B. truncatus* is the main vector in N. Africa and Mediterranean area, parts of Asia, E. African highlands and S. Africa as far as Cape Peninsula. Throughout this area *S. hæmatobium* will not develop in *B. africanus*. In the south this latter is the vector and the distribution of the disease in the Cape Province is identical with that of *B. africanus*).

(Annandale and other conchologists consider that the three species *B. contortus*, *dybowskii*, *innesi*, are subvarieties of *B. truncatus* (Audouin, 1809) syn. *B. contortus*.)

SCHISTOSOMA INTERCALATUM (Fisher, 1934).—Synonym *Bilharzia intercalata*. The eggs of this species were first found by Chesterman in 1923 and recognized as a new species by Fisher from the Upper Congo (Yakusu). Subsequently it was regarded as dubious, though reported from Gaboon by Zellweger, until the discovery was confirmed in every detail by Schwetz with cercariæ obtained from Stanleyville (1951). An endemic focus has been found in Libreville (Congo) by Labouel and it is now known to occur in the French Congo as well as in S. Nigeria. This species closely resembles *S. hæmatobium*, being half-way between it and *S. bovis*, differentiated mainly by the size and shape of the egg (Fig. 302). The eggs are found mainly in the fæces, very rarely in the urine; in this respect it resembles *S. mansoni*. The male has 4–6 testes. Schwetz succeeded in infecting mice with cercariæ from *Bulinus africanus* sent from Stanleyville to Antwerp. From the fifty-first to fifty-eighth day he obtained adult schistosomes which resembled those described by Fisher. With miracidia hatched from eggs derived from mouse fæces and from their livers he succeeded in infecting *B. africanus* in the laboratory. The snails began to shed cercariæ between the sixty-third and eightieth day. With these he confirmed the original discovery, produced further infections in mice and again recovered the adult forms. *S. intercalatum* then belongs to the same group as *S. hæmatobium*. A sheep has been infected. Pitchford (1959) suspects hybridization between *S. hæmatobium* and *S. bovis*.

SCHISTOSOMA MANSONI (Sambon, 1907)

Synonym.—*Bilharzia mansoni* (Fig. 303).

Distribution.—Africa generally—especially Egypt, Congo, Gambia and West Africa, East Africa, Eritrea, Abyssinia, Zanzibar, Rhodesia, Tanganyika, Kenya, Uganda, Madagascar, Natal, Transvaal, South America (probably imported by African slaves), Brazil, Venezuela, Guianas, West Indies (Antilles, especially Antigua). In St. Kitts the green monkey (*Cercopithecus sabæus*), introduced from Africa, is naturally infected and constitutes a reservoir for man; in Kenya and Uganda the baboon (*Papio doguera*) and in W. Africa *Papio papio*. Guinea-pigs, mice, hamsters, hedgehogs, armadillo, multimammate mouse, house-rats in the Congo, Cebus monkeys, the Coati, opossums and the Agouti can be infected in the laboratory, but the infected guinea-pig never discharges eggs in the

fæces. In Sierra Leone, infection is commoner in adult women than in children or in men. The subspecies discovered by Schwetz in rodents in the Belgian Congo is known as *S. mansoni rodentorum*.

Characters.—*Male* measures 1·1–1·2 cm. by 1 mm. and in its main structure is similar to *S. hæmatobium*, but with its ventral sucker and wart-like tuberculations larger and more pronounced (Fig. 178, p. 706). The intestinal canal bifurcates

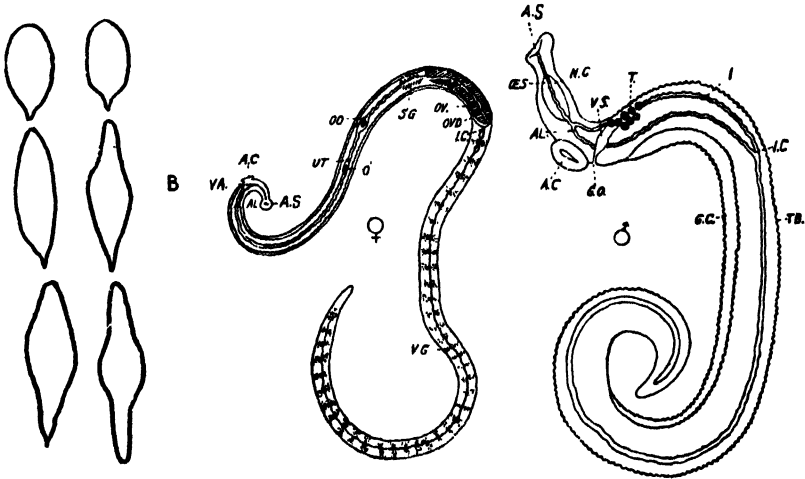


Fig. 302.—Outline drawings of eggs of
(A) *S. hæmatobium* ;
(B) *S. intercalatum* ;
(C) *S. bovis*. (After
A. C. Fisher.)
Drawn to scale.

Fig. 303.—*Schistosoma mansoni*. × 10.

(For lettering, see inscription to Fig. 299A; o', lateral-spined egg.)

at the level of the ventral sucker. The intestinal caeca unite in the anterior half to form a long, single, intestinal tract. There are 8–9 small testes with corresponding vasa efferentia opening into the vesicula seminalis. The size of the female is 1·2–1·6 cm. by 0·25 mm.; as in the male, the intestinal caeca unite in the anterior half, where the ovary is also found, in front of the union of the intestinal caeca. The uterus is short and contains a few (usually only one) lateral-spined eggs. The shape of the bulb of the shell gland determines the shape and position of the spine. The yolk glands occupy two-thirds of the body at the posterior end. The anatomy is otherwise as in *S. hæmatobium* (q.v.). Hermaphrodite and bisexual males are found in hyperendemic infections and in unsuitable mammalian hosts.

Living, mature worms are essential for the sexual maturation of the female of *S. mansoni*. The principal, and probably the only stimulus, to sexual maturation of females is provided by the products of males in the act of copulation (Berberian).

Adult *S. mansoni* can be maintained alive *in vitro* in horse or human serum. The worms were seen to copulate and produce ova *in vitro*. Reduction of temperature to 20° C. for 12 hours had no harmful effect.

Habitat.—It lives in the venous system, especially the inferior and superior mesenteric veins, the hæmorrhoidal plexus and the portal system. If, at autopsy, venous blood from the liver is squeezed out on the side of a glass vessel, the

schistosomes adhere, and can be picked off. The eggs are deposited in the sub-terminal branches of the mesenteric veins (Fig. 304) where, aided by the lateral spine, the ovum escapes (*see also* p. 706). In the bowel some pass through the muscularis mucosæ *via* the capillaries; when present in large numbers, they produce acute dysenteric symptoms.

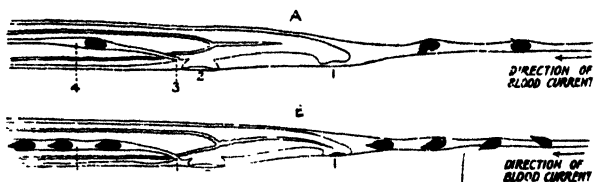


Fig. 304.—Diagram representing deposition of eggs by (A) *S. mansoni* and (B) *S. haematobium* in blood-vessels, and their passage to exterior.

1. Anterior sucker; 2. posterior sucker; 3. vaginal orifice; 4. uterus with contained eggs.

The egg measures $150\ \mu$ by $60\ \mu$, the lateral spine $20\ \mu$, but there is considerable variation. Immature specimens in intestinal lesions differ from eggs found in the faeces in being smaller. The miracidium is similar to that of *S. haematobium*, but may be larger. If the faeces are diarrhoeic, the miracidium often escapes in the lumen of the bowel.

Life-history.—The sporocysts are convoluted thin-walled sacs within the head-foot region of the snail and each contain 200–400 daughter sporocysts. Each miracidium carries 50–100 germinal cells which divide to produce anything up to 200–500 sporocysts.

The daughter sporocysts leave the mother sporocysts and migrate to the digestive gland. On reaching the location the daughter sporocysts enlarge and give rise to cercariæ. Most are derived from separate germinal cells carried by daughter sporocysts (a process known as polyembryony). Cercariæ of *S. mansoni*, under normal conditions, emerge from the molluscan host between the hours of 9 a.m. and 2 p.m. Exposure to a strong artificial light and a raised temperature increases the output. At continuous low temperature passage of the schistosomes in snails results in low cercarial production by the sporocyst and their infectivity for mice is lowered. Rats are more resistant to schistosome infection than are mice, and less so cotton rats. With unisexual infection mice live without symptoms. With a virulent strain of *S. mansoni* successful infection follows exposure to 20–50 cercariæ, though after exposure to an even greater number, there is no increase in the ultimate number of adults. The cercariæ were thought to differ in the two species, but this is probably not correct, but according to Faust, on the whole these cercariæ have somewhat smaller bodies and longer tails than those of *S. haematobium*. Standen has found that penetration is effected by a combination of lytic and mechanical means. With a maximum of lytic effect against those tissues which offer the greatest resistance, cercariæ penetrate between the hair follicles, the tail may be carried down with hypodermal tissue before detachment. After reaching a lymphatic vessel cercariæ enter it and so gain entry to the venous circulation. After penetration, they take six weeks to mature. The eggs are laid mostly in the portal system, eventually passing through the intestinal mucosa to escape in the faeces. Vogel has succeeded in infecting *B. pfeifferi* with a single miracidium. The proportion of the sexes eventually produced from cercariæ derived from a single miracidium is equal. Standen has proved that when an established infection of one sex is crossed with cercariæ of the opposite sex, bisexual infections develop. In all-male infections a variable proportion of the schistosomes migrate to the mesen-

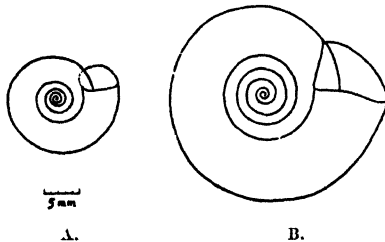
teric veins by the tenth week, but no such migration takes place in all-female infections as showing that the male possesses migratory impulses which are absent in the female. In female infections they remained immature till a male infection was introduced. The essential factor controlling the time of migration of paired worms is the attainment of maturity of the female. Development takes place mostly in molluscs of the genus *Planorbis*, now known as *Biomphalaria* (Fig. 305).

AFRICA, MADAGASCAR, ARABIA

- Biomphalaria boissyi*—N. Africa, S. Arabia (Fig. 305A).
B. sudanica) Sudan, Oubangui—Chari, N.E. Congo, Uganda,
B. sudanica tanganikana) Tanganyika
B. pfeifferi) S. Africa, S. of Equator, Madagascar, N. & S.
B. pfeifferi gaudi Gambia) Rhodesia.
B. nairobiensis—Kenya, Tanganyika, parts of Belgian Congo.
B. rüppelii—Sudan, Eritrea, Somaliland and S.W. to Angola.
B. adowensis—Eritrea, Kenya and Uganda.
B. salinarum—Angola and S. Belgian Congo.
B. choanomphala—L. Victoria and L. Kyoga.
B. stanleyi—L. Albert.
B. kivuensis—L. Kivu.
B. smithi—L. Edward.
B. germaini—L. Chad and French W. Africa.

CENTRAL AND S. AMERICA

- Biomphalaria glabrata* (*Planorbis guadeloupensis*)—S. America, W. Indies (Fig. 305B).
B. olivaceus—Brazil, Dutch Guiana.
B. centimetralis—Brazil.
B. havanensis—Cuba.



Biomphalaria boissyi (*alexandrina*). *Biomphalaria glabrata*
 Fig. 305.—Molluscan hosts of *S. mansoni*. (C. J. Hackett.)

Mandahl-Barth (1958) has shown that *boissyi* should not be applied to this species, and that *B. alexandrina* (Ehrenberg, 1831) is correct.

It is now agreed that the genera *Australorbis*, *Afroplanorbis* and *Tropicorbis* are synonyms of *Biomphalaria*. Parænze (1958) considers all these genera synonymous and the correct original generic name should be *Taphius*.

Cram and colleagues (1944) have demonstrated that *Tropicorbis havanensis* and *Drepanorema cultratus*, widely distributed in Louisiana, Texas and Cuba, are good laboratory hosts of this parasite which does not occur there. Files and Cram suggest that there are physiological varieties of the same snail which affect their capacity to act as intermediary hosts. Brazilian *Biomphalaria glabrata* differ from the same species from Venezuela and Porto Rico. The contrast

between the susceptibility of *Biomphalaria pfeifferi* from Liberia and *B. boissyi* from those in the W. Hemisphere supports the theory that this parasite was originally imported from W. Africa. Local strains of *S. mansoni* develop freely in *B. glabrata* from Porto Rico. Morphologically identical strains of this snail from São Paulo are refractory (Newton). It is suggested that susceptibility to *S. mansoni* infection is a heritable factor and that several genetic factors are involved.

Papirmeister and Bang have demonstrated that when cercariæ of *S. mansoni*, newly emerged from *Biomphalaria glabrata* are, exposed to diluted serum from monkeys or patients with schistosomiasis a precipitate forms around them.

Hyaluronidase is an enzyme which is elaborated by certain bacteria by means of which they are able to spread in the tissues. This ferment (Levine and others) can be detected in *S. mansoni* cercariæ; but it is not claimed that it is the only enzyme concerned in cercarial penetration of the skin.

SCHISTOSOMA JAPONICUM (Katsurada, 1904)

Synonym.—*Bilharzia japonica* (Fig. 306).

Distribution.—Japan (Yangtse, North River, Yunnan), Upper Burma, South Philippine Islands (Samar and Leyte), Celebes (Lake Lindoe): in restricted endemic foci. In Formosa a non-human strain occurs also as a natural infection in the cat, pig, dog, horse and cattle. It can be transmitted to monkeys, rabbits, hamsters, mice, rats and guinea-pigs. A race of non-human *S. japonicum* is recognized in Formosa in domestic animals, especially in pigs by Hsii and in 8.6–21.5 per cent. of wild rodents.

Hsii and Li (1958) have shown that in Formosa the shrew, *Crocidura murina*, acts as a host reservoir of *S. japonicum*.

Characters.—The male measures 9–12 mm. by 0.5 mm. and has 6–8 elliptical testes situated dorsally to the ventral sucker. The vasa efferentia join to form a common duct opening posterior to it. There is a large seminal vesicle. The posterior portion of the fluke widens out, and the sides overlap more extensively than in other species. There are no tuberculations.

The female measures 1.2–2.6 cm. by 0.3 mm. but shows variations in size. The ovary is centrally situated, and the intestinal cæca unite immediately behind it. Well-developed yolk-glands extend to the posterior extremity. The uterus also is well developed and wider than in other species. It contains 50 or more eggs in two rows.

The general anatomy differs mainly from other species in the smaller size and absence of tuberculations. Suckers are placed close together at the anterior extremity, the ventral one (*acetabulum*) being pedunculated and funnel-shaped. Suckers and ventral surface are covered with small spines. Both suckers are larger than those of *S.*

hæmatobium. The cesophagus has two bulbs; the bifurcation of the intestinal canal

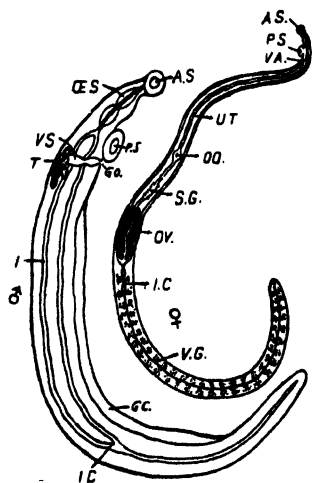


Fig. 306.—*Schistosoma japonicum*, male and female. $\times 10$.

A.S., Anterior suckers; G.C., gynæcophoric canal; G.O., genital opening; I., intestine; I.C., union of intestinal cæca; C.S., cesophagus; O.O., oötype; OV., ovary; P.S., posterior sucker; S.G., shell-gland; T., testes; V.A., vagina; V.G., vitelline glands; V.S., vesicula seminalis.

takes place at the level of the ventral sucker, but the cæca join more posteriorly, the united gut occupying usually nearly half the body length. The excretory system consists of two longitudinal canals opening dorsally by an excretory pore.

In *utero* the egg measures 60–80 μ by 40–60 μ , but when in fæces, 70–100 μ by 50–65 μ , is oval and practically spineless, but there is a rudimentary knob-like lateral spine in a small depression of the shell (Plate XXVII, 13). They are extruded into the blood vessels, and are found chiefly in the intestinal walls, liver, pancreas and mesenteric glands and brain. They may not be found in the fæces, but may be present in the duodenal contents. When they are passed into water with the fæces they hatch into ciliated miracidia. The cephalic glands of the miracidium are smaller than those of other species. According to Vogel, the maximum life-span of the egg is 21 days, of which development occupies 9–10 days. The mature miracidium inside the egg lives about 12 days

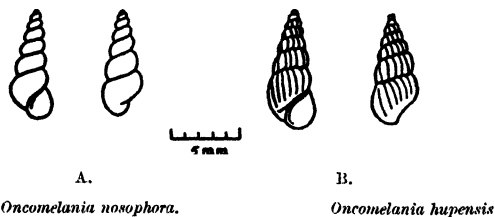


Fig. 307.—Molluscan hosts of *S. japonicum*. (C. J. Hackett.)

Habitat.—Large numbers have been found in man at autopsy and 20,000 have been recorded in an experimentally infected horse. This schistosomine inhabits the veins of the large intestine, the gastric, superior mesenteric, splenic and cardiac veins, occasionally also the pulmonary arteries, but rarely any others. It commonly inhabits the veins of the small intestine and in this respect differs from the other two human species. An infection of over 30 years standing was found in an officer in whom no ova could be demonstrated in the fæces without *eosinophilia*, but viable eggs of *S. japonicum* were present in a biopsy of the liver.

Life-history.—This is similar to that of the preceding species. Losing its cilia, the miracidium in the ymph spaces of the head and foot of the snail, after seven days becomes a sporocyst in the liver and hermaphrodite gland of a snail, *Oncomelania* (several species, Figs. 307, 308). The delicate, elongated, finger-like sporocysts each produce 50 or more daughter-sporocysts. Cercariæ are similar to those of other species, but are said to be smaller (0.48 mm. by 0.05 mm.) (Fig. 309) and the oral sucker is greatly developed. They are produced sixty days after infection, are phototactic and unable to survive a temperature above 50° C. or below 2° C. Discharge of cercariæ from *Oncomelania quadrasi* takes place largely at night and continues for 2–3 consecutive nights (Ingalls). The critical factor appears to be the alkalinity of the water—pH 7.0. The cercariæ escape into water, and penetrate the skin; subsequently minute flukes (schistosomula), measuring 150 μ , can be found in the liver. They attain maturity in 30 days, and in 35 days eggs appear in the fæces. These reach the lungs through the pulmonary arteries, and travel via the mesenteric arteries and veins and portal vein to the liver. The molluscan hosts belong to the genus *Oncomelania* (Gredler,



Fig. 308.—*Oncomelania hupensis* with operculum.

state of confusion that there is no certainty that scientists using the same name are, in fact, referring to the same snail.

More extended studies are necessary and snails have to be studied as such, and not as intermediaries of the schistosomes. Identification must be based on the internal anatomy of the snails as well as on their shells. Physiological and biochemical factors may also come into the picture.

Hubendick thinks that experimental interbreeding remains the only absolute criterion of species in closely related forms, but mating discrimination in species of *Limnaea* and *Biomphalaria* is not always strict and self-fertilization is extensive, so that reliable demarcation of species may come from chromosome studies, or from serological diagnoses. In land snails there are a small number of species which have a vast geographical range and in which there are numerous well-isolated populations, resulting in great intra-specific variation. Anatomically the organs of the mouth and alimentary canal may occasionally be useful. The radula, on account of intraspecific variation, is not of great use in classification below the level of genera. The reproductive system may be most useful, but here also specific characters may be obscured by stages in growth, by maturation and by variation.

Schistosome cercariae.¹—These consist of a body and elongated forked tail (Fig. 309), measuring 0.48 mm. in total length. The head and tail are approximately of equal length. The cuticle is beset with microscopic spines. It has an anterior urn-shaped oral, and median muscular, ventral sucker; the former is larger. The central part of the body is occupied by the oral glands and a mid-line cesophagus, on either side of which are the ducts of conspicuous peri-acetabular glands, opening by small retractile papillae surrounding the mouth. It has been shown that the peri-acetabular glands are connected with the penetration of the skin. Contraction of the circular muscles compresses the ducts and expresses the secretion, enabling the cercaria to burrow into the tissues. The mouth opening is small, oval and placed on the anterior surface. The cesophagus is situated at the lower pole. The ventral sucker is covered with small spines pointing to the periphery. There are five periacetabular glands, having large clear cells, with conspicuous nuclei and acidophil protoplasm. There is a primitive nerve ganglion anterior to the central sucker. The posterior genital centre consists of a mulberry mass of cells.

The excretory system consists of four pairs of flame-cells on the margins of the body; the canals form collecting tubules of greater calibre running forwards and backwards, to meet at the posterior end of the body. The duct is continued through the tail where there is one pair of flame cells.

All cercariae are "phototactic," emerging from the snail in sunlight between 9 a.m. and 2 p.m., and do not emerge on dark days; some 50 to 1,000 may be discharged daily. The optimum temperature for most species is 32–33° C., but for *S. mansoni*, 15–35° C. An abundant supply of oxygen is necessary for their survival. The lips of the oral sucker are extended or retracted to assist in entering skin. Cercariae cannot feed. In water they swim with ease, moving by the tail and body, in a circular movement propelling towards the tail. They rest with the prongs of the tail on the surface, and then slowly sink; they then absorb oxygen through the tail, then rise again. The total life-span is 5 days; they are infective for 3, becoming motile when the water is disturbed. They adhere to the side of the vessel by the ventral sucker and, when they fix on to an object, they elongate. Movement on a fixed surface is effected by releasing the ventral sucker, contracting the body, and then affixing themselves by the oral

¹As many as 300,000 may be discharged, and the cercariae are all of one sex. The metacercariae (or schistogamulae) are carried to the lungs and remain there long enough to squeeze through the capillaries in order to reach the pulmonary veins. Only those which leave the aorta by the oesophageal axis or mesenteric arteries and reach the liver via the portal vein survive.

sucker. Warmth appears to be the chief factor in attraction to a host. When they contact it, they cast off their tails, pierce the epithelium, lose the cephalic glands, and become a *schistosomulum*. The cercariæ come into contact with the skin at the surface film and, as the water evaporates, they enter the skin. Adult schistosomes are found in the portal vein within six weeks.

There is no general agreement on the different minor details in the structure of the three human species; probably there are individual differences in various batches. The average size is 0.4–0.5 mm. in total length; on the whole, cercariæ of *S. japonicum* are smaller than others, with measurements as follows: Body, 100–160 μ in length by 40–66 μ in transverse diameter; tail trunk, 140–160 μ in length by 40–66 μ in diameter; furca, 56–75 μ long. All kinds have 5 or 6 pairs of salivary-mucin peri-acetabular penetration glands.¹ Innumerable trematode cercariæ are found in freshwater snails in tropical countries. The life-history of many is unknown. All schistosome cercariæ of man, mammals and birds have forked tails.

C. elvæ is found in Lake Michigan and in several Minnesota lakes and is a schistosome cercaria (non-mammalian) emerging from *Limnæa stagnatilis* var. *appressa*. It produces a papular eruption in bathers. *C. ocellata* (Taylor and Baylis) produces "swimmers' itch" in Roath Lake, near Cardiff, emerging from *L. stagnatilis* at certain times of the year. It is probably a schistosome parasite of a water fowl. Other species are *C. douthitti*, *C. physellæ* and *C. stagnicola*. The rash consists of blotchy papules with a central puncture (p. 653). In Malaya and India a similar rash is produced sometimes by cercariæ of *Schistosoma spindale* of the Indian water buffalo.

In the lower Ottawa River *Trichobilharzia cameroni* is the cause of swimmer's itch. It is a parasite of ducks and develops in a snail, *Physa gyrina*. *Microbilharzia variglandis* is another avian schistosome, whose larvæ produce "swimmer's itch" on ocean beaches in Narragansett Bay; in E. Florida and S. California the cause is *cercaria littoralinæ*. Sea-bathers are also attacked with swimmer's itch by *cercaria huttoni* which emanates from the marine snail—*Haminaea antillarum guadalupensis* in the Miami district of Florida.

Superfamily: PARAMPHISTOMATOIDIA (AMPHISTOME TREMATODES)

Genus: *Gastrodiscoides*

Gastrodiscoides hominis (Lewis and MacConnell, 1876); Leiper, 1913.

Distribution.—Malaya, Assam, India, Burma, Cochin China, British Guiana. In Kamrup District, Assam, 41 per cent. of the population are infected; in Burma 5 per cent. The normal host is the pig or the mouse-deer.

Characters.—The fluke is reddish from hæmoglobin pigment. When alive, it is very expansile and can elongate to 1 cm. Preserved specimens measure 5–7 mm. by 3–4 mm. at the widest point. The anterior end is conical, the posterior discoidal flattened ventrally to form a concave disc. Prominent genital papillæ are seen, and the common genital pore is 2.5 mm. from the oral sucker. The ventral sucker (acetabulum) is ventrally situated in the caudal portion and measures 2 mm. in diameter. The cuticle is smooth. The alimentary canal consists of a pharynx with two pear-shaped pharyngeal pouches. The oesophagus is 1 mm. in length, and ends in a muscular bulb where the bifurcation of the intestine takes place and cæca run back to the edge of the acetabulum. There are two lobulated testes placed diagonally between the intestinal cæca. A seminal vesicle is present, but no cirrus. The ovary lies in the midline, posterior

¹ Faust stated that the cercaria of *S. hamatobium* has 2 anterior pairs with oxyphilic and 3 posterior pairs with basophilic granules; those of *S. mansoni* 2 anterior oxyphilic and 4 posterior basophilic; and those of *S. japonicum* 5 pairs with fine oxyphilic granules.

to the testes. An ovoid shell gland is placed near the ovary with a *receptaculum seminis* anterior to it. The uterus is short. Laurer's canal is present. The vitellaria lie in the mid-third. The ovoid egg measures $152\ \mu$ by $60\ \mu$ and has an operculum. Development outside the body takes place in a snail, probably *Cleopatra bulimoides*. The cercariæ probably encyst on vegetation.

This fluke lives in the cæcum in large numbers and usually produces no symptoms. Thymol, carbon tetrachloride and tetrachlorethylene are effective in treatment.

Genus: *Watsonius*

Pseudodiscus (Watsonius) watsoni has been found in large numbers in a negro in South West Africa (1904). Its normal hosts are monkeys of the genera *Cercopithecus* and *Papio* (baboon).

PHYLUM PLATYHELMINTHES

CLASS: CESTOIDEA (kestos = a girdle) or TAPEWORMS

The head of these worms develops from the end of the embryo opposite to the head, and shows independent co-ordinated movement. The *strobila*, or segments, have their own musculature, which relieves the strain on the head. The worms can live for several years. They absorb nutriment through the cuticle. They are hermaphroditic, the male segments fertilizing the adjacent female. Male organs develop before the female.

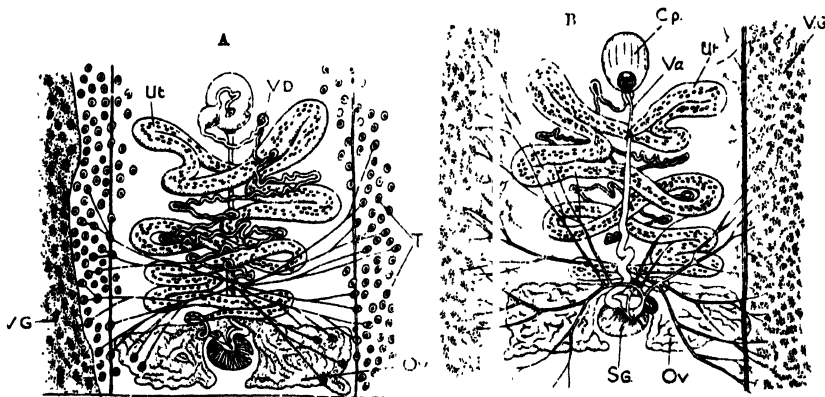


Fig. 310.—Mature segment of *Diphylobothrium latum*. (After Sommer and Landois, in Brumpt's "Précis de Parasitologie.")

A, Dorsal, or male aspect. T, testes; V.D., vas deferens; V.G., vitelline glands.
B, Ventral, or female aspect. C.p., cirrus pouch; Ov., ovary; S.G., shell-gland; Ut., uterus; Va., vagina; V.G., vitelline glands.

Human cestodes are divided into two orders:

1. *Pseudophyllidea*, with slit-like suckers, oval head, two long grooves with muscular walls, no hooks, and the genital orifice on the flat surface.
2. *Cyclophyllidea*, cup-like, or round suckers; genital orifice marginal.

ORDER I: PSEUDOPHYLLIDEA

Genus: *Diphylobothrium*

DIPHYLOBOTRIUM LATUM (Linn. 1758)

Synonym.—*Dibothriocephalus latus* (Fig. 310). "Broad Tape Worm."

Distribution.—It lives in the small intestine of man, the dog, cat, bear, walrus, sea-lion, fox, mongoose, mink, leopard, clouded leopard, and pig.

and is found in Sweden, Russia, Switzerland, Rumania, Turkmenistan, Japan, Madagascar, the Central African lakes, and in the rivers Erne and Shannon in Eire (Ireland). In recent years it has been introduced into several big North American lakes, especially Lake Michigan, where it is known as the "Broad fish tapeworm." In Finland the worm is very important and it is estimated that 14 per cent. or 600,000 people harbour this parasite. It has been found to be widespread in E. Canada and some 11.4 per cent. of the population in N. Alberta harbour it, also in Canadian and Alaskan Eskimos. A new focus has been discovered in Lake Colico, in Chile.

Characters.—It is greyish and more translucent and less fleshy than *Tænia* and may attain a length of 3–10 metres, lying coiled up in the small intestine. Multiple infections are common. The scolex (3 mm.) has no rostellum or hooklets, but two slit-like suckers with longitudinal grooves (bothria). The neck is thin; the proglottides number 3,000–4,000. The number of worms corresponds to the individual plerocercoids swallowed (Leiper). Mature segments are broader than they are long. A single worm may discharge as many as from 36,000 to a million eggs *per diem*. It may be discharged from the bowel naturally, without treatment. (For details of anatomy of male and female elements, *see* Fig. 310.)

The egg is operculated, with a brown shell, measuring 70μ by 45μ (Pl. XXVII, 21). No segments are passed in fæces (unlike *Tænia*). The eggs, discharged by the uterus to the exterior, are found in vast numbers in the fæces, occupying one third of their bulk. The yolk-cells are tightly packed, crowded with steel-grey granules (thus differing from trematode eggs).

Life-history (Fig. 311), Rosen and Janicki, 1918. — The egg is passed in water; when the operculum is lifted, the ciliated six-hooked *coracidium* emerges; resembling a ball ($22\text{--}30\mu$), it swims by means of its cilia, but dies in 24 hours. Normally it is swallowed by fresh-water crustacea, the first intermediary—*Cyclops strenuus*, *Diaptomus gracilis*.

D. graciloides or *D. oregonensis*, *Cyclops brevispinosus*, and *C. prasinus* in U.S.A. The outer layer is then digested. The hooks tear a hole in the gut wall; it passes into the body cavity and may kill the

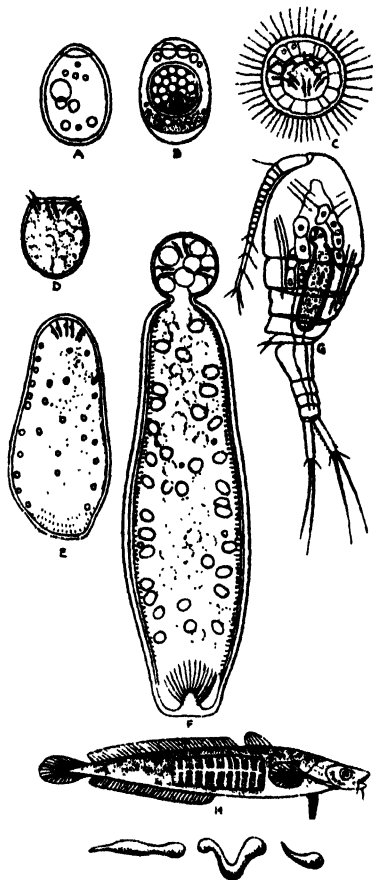


Fig. 311.—Evolutionary cycle of *Diphylobothrium latum*. Drawn to different scales. (Partly after Brumpt.)

A, Egg of *D. latum*; B, hexacanth embryo; C, ciliated oncosphere or coracidium; D, E, F, development of larva, or proceroid, in *Cyclops*; G, proceroid in body-cavity of *Cyclops*; H, development of plerocercoids in fishes; I, plerocercoids of different shapes, ingested by man, dog, or cat.

cyclops. Lying outside the gut wall it becomes the *proceroid larva* (Fig. 311, d, e, f) which is ovoid, 50–60 μ long, with a terminal spherical appendix and six hooklets in the terminal appendage or *cercomer*. At most two of these are found in one cyclops, which is then swallowed by fresh-water fishes of many species, the second intermediaries—pike, perch, salmon, trout, grayling; in Africa the barbel; in U.S.A. the pike, wall-eye and burbot. Reaching the stomach of the fish, the proceroid penetrates to the body cavity, and, after three to four days there, encysts as a plerocercoid or *sparganum* (6 mm.) in the muscular and connective tissues. Sucking, cephalic grooves, nervous and excretory systems are developed. It is then ingested by man with raw roe (caviare) or insufficiently cooked fish and the *plerocercoid* develops in five to six weeks into an adult *Diphylllobothrium*. Fresh-water fishes harbour other spargana which cannot be differentiated in this stage.

N.B. The process of “kippering” does not kill the plerocercoids, and ordinary smoking is ineffectual, but brine saturation is effective. This tapeworm can live as long as 29 years (Riley, 1919).

Pathogenesis and treatment.—Symptoms are usually trifling; there is early eosinophilia in a small percentage and even sometimes severe pernicious anæmia. Dried or alcoholic extracts of the worm cause destruction of red blood corpuscles, but not proportionately of the hæmoglobin. The anæmia is apparently due to the presence of the worm in the jejunum where it interferes with the production of the intrinsic factor. Von Bonsdorff (1955) thinks that the hel-

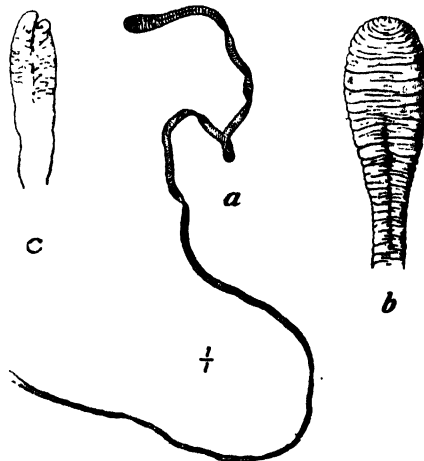


Fig. 312.—*Diphylllobothrium mansonii* plerocercoid, extracted from an abscess in a Masai. (After Sambon.)

a, Natural size; b, anterior extremity; c, posterior extremity.

minthic anæmia is identical with the classic disease, except that it may also occur in young subjects and the gastric juice contains Castle's intrinsic factor and frequently also HCl. *D. latum* contains considerable amounts of vitamin B₁₂, so that aqueous extracts of the dried worm, when injected parenterally, bring about maximal hematological remissions and improvement of neurological disturbances. The worms are expelled by flix mas, stebrin, hexylresorcinol-tetrachlorethylene, or oleoresin of aspidium. There are records of hundreds of feet of worms expelled after anthelmintic treatment without any associated

symptoms, but Tarassov (1937), who experimentally infected himself, had marked abdominal pains and loss of weight.

Diphylobothrium minus is a small variety which the Russians claim as a separate species. It has been found in Lake Baikal and has a similar life-history to that of *D. latum*. Its second intermediary hosts are various species of salmon and grayling which are eaten salted or frozen by Mongolian peoples.

D. alascense is a new species amongst the Eskimos and is differentiated by the form of the scolex. The plerocercoids probably occur in two species of fish—*Pungitius* and *Dallia* (Rausch and Williamson, 1958).

DIPHYLOBOTHRIUM MANSONI (Cobbold, 1882)

Synonym.—*Dibothriocephalus mansonii*, *D. houghtoni*.

Distribution.—Japan, China, East Africa, Australia and British Guiana. The adult form is found in the dog, wolf, fox, cat, leopard and tiger, and its plerocercoid in man, frogs and snakes.

Characters.—It resembles *D. latum*, is 6–10 m. long, and has a more delicate structure with a narrower and more ellipsoid egg than *D. latum*.

Its plerocercoid was named *Sparganum mansonii* by Cobbold. It was first found by Manson in 1882 at the autopsy of a Chinese. Since then 60 cases have been reported. The life history was worked out by Yoshida, and later by Okumura.

Life-history.—The adult stage occurs in the dog and other animals, the plerocercoid under natural conditions in the frog (*Rana nigromaculata*), or snake (*Elaphe climacophora*). The proceroid in *Cyclops leuckarti* shows the same stages as in *D. latum*.

Man is infected by accidentally swallowing a proceroid whilst drinking, thus becoming a second intermediary. The Chinese custom of applying raw split frogs to sores on the hands may be a chief portal of entry there. The sparganum in man measures 8–36 cm. by 0.1–1.2 mm. by 0.5–1.75 mm. thick (Fig. 803). Its body is flat and transversely wrinkled, with a longitudinal median groove. It is found in many parts of the body: kidneys and iliac fossæ, pleural cavities, urethra and subcutaneous tissues.

Ocular sparganosis in Tonquin (Casaux) is now becoming commoner. The plerocercoid gets into the orbit and causes pain, redness, cedema of the eyelids, lacrymation and ptosis. It has been found under the conjunctiva in Japan and China—probably also as a result of split-frog poultices, made from the tree frog (*Rana limnocharis*).

Treatment.—Intravenous neosalvarsan, 0.3–0.45 gm., is given, and repeated in four to five days. Tarsorrhaphy should be performed to preserve the cornea until the worms have been killed.

Spirometra mansonioides, or *S. houghtoni*, an aberrant form found in cats and dogs in U.S.A., was differentiated by Mueller from *D. mansonii* by the poorly-developed bothria. The scolex measures 0.2–0.5 mm. as against 0.4–0.8 mm.

S. mansonioides (Mueller, 1935) has now been found to be the parent form of *Sparganum proliferum* (Ijima, 1905) (Fig. 313). *S. mansonioides* is found in the intestine of the cat in the Southern United States, and is separable from *D. latum* and *D. cordatum* by the scolex, uterine characteristics and smaller size. Specimens vary from 20–60 cm. in length, but may attain 1 m. by 8 mm. Immature proglottides number 200–300.

The egg is pointed, 65 by 37 μ , with a conical operculum. The life history is as in *D. latum*.

The plerocercoids (*sparganum*) measure 3–12 mm. by 2.5 mm. (Fig. 313) and are contained in cysts, which are found in man in Japan and Florida. The body contains calcareous corpuscles. The cysts became disseminated throughout the body in the subcutaneous tissues, intramuscular fasciæ, walls of the alimentary canal, mesentery, kidney, lung, heart and brain. The prognosis in man is grave. Similar plerocercoids have been reproduced in macaque monkeys.

Sparganosis has been found in Korea and spargana, 23–50 cm. in length, removed from the muscles of the abdomen and chest. All had eaten raw snakes—*Dinodon rufozonatum*. It has also been found in abscess of the leg. The adult form is *Dibothriorhynchus decipiens* (Osmani and Peyrallo, 1955). A new species, *D. sp.*, type, *grossum*, has been reported by Heinz from S Africa (1955).

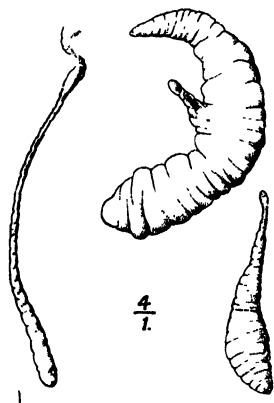


Fig. 313.—Different forms of *Sparganum proliferum*. (After Ijima.)

ORDER II: CYCLOPHYLLIDEA.

Genus: *Tænia*

TÆNIA SOLIUM (Linn, 1758), "Pork tapeworm." (Fig. 315.)

Distribution.—This is world-wide, co-extensive with the intermediary, the pig. The worm is unknown among Mohammedans and Jews, and is rare now in England, owing to meat inspection.

Characters.—It lives in the upper third of the small intestine. The name "*solium*" is derived from the resemblance of the rostellum to the conventional figure of the sun. It attains a length of 2–3 m.—exceptionally 8 m., having 800–1,000 segments. The head is globular, quadrangular, 1 mm. in diameter, and the rostellum short and pigmented, with a double row of 20–50 hooklets (Fig. 314, 3). The four suckers project slightly and are circular, measuring 0.5 mm. in diameter. The anterior proglottides are small, broader than they are long, the more mature ones measuring 12 mm. by 6 mm. Each proglottis has a marginal genital pore with thick lips; its situation alternates irregularly between the right and left

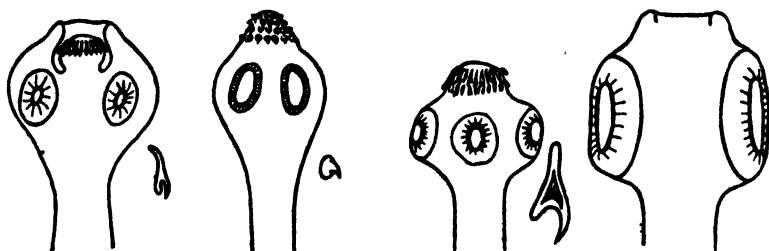


Fig. 314.—Heads of human cestodes, showing suckers and, when present, arrangement of hooklets. Diagrammatic.

1, *Hymenolepis nana*; 2, *Dipylidium caninum*; 3, *Tænia solium*; 4, *Tænia saginata*.

margins. The uterus is median with 7-10 stout diverticula (Fig. 315A). The testes consist of 150-200 follicles, distributed throughout the dorsal plane. Proglottides number less than 1,000. Terminal ripe segments pass out in the faeces and have an independent movement which enables them to migrate outside the anus. Each gravid segment contains from 30,000 to 50,000 eggs.

The egg measures 31-56 μ in diameter, and is round with no operculum. It has two radially-striated shells, the inner formed by the embryo (thus differing from pseudophyllidea), and a vitelline membrane when it is in the segment which is lost in the faeces. Small numbers of eggs are found in the faeces when the segments break. They contain the six-hooked onchosphere (Pl. XXVII, 16).

Life-history.—Mature segments are detached and pass out with the faeces; they disintegrate and the eggs are set free and eaten by the intermediary host (the pig). Man is occasionally infected by cysticerci (see cysticercosis, p. 803), so are other primates, occasionally sheep or dogs. The onchosphere penetrates the gut wall and enters the bloodstream, settling in the muscles, especially the heart, where it loses its hooks, and becomes a *cysticercus* (5-20 mm.). Known as *Cysticercus cellulosae*, it has a small, invaginated scolex and a neck, resembling a miniature adult tænia. Infected pork is popularly known as "measly pork." In prevention thorough cooking of pork is essential. At 0° C. the cysticerci can persist for 70 days.

In the alimentary canal of man, or other definitive host, the bladder of the cysticercus is absorbed by the gastric juices; the scolex and head are evaginated and then pass to the small intestine, where the scolex fixes itself to the gut wall and forms proglottides. In man, cysticerci are found in the tongue, neck, ribs, liver, heart, lungs, brain and eye, where they may persist for 20 years. Epileptiform convulsions are frequently produced (p. 803). Larvæ may develop from viable eggs in the gut as an accidental infection, or auto-infection in persons infected with adult tænia. Clinically, this variety of bladder-worm is sometimes known as *Cysticercus racemosus*.

Pathogenesis.—*T. solium* usually produces no symptoms, but in debilitated persons or in children it may cause gastro-intestinal disturbances such as anorexia, vomiting, nervous symptoms and even anæmia. (For treatment, see p. 801.)

TÆNIA SAGINATA (Goeze, 1782) "Beef Tapeworm." (Figs. 314, 315)

Distribution.—This is world-wide, wherever ox-meat is eaten; the worm is

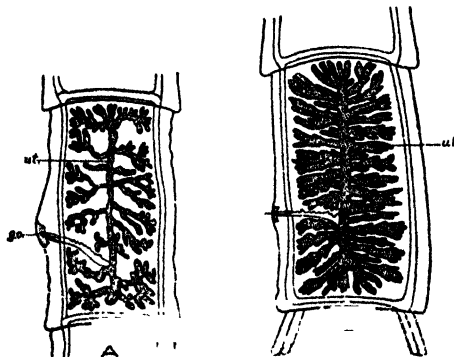


Fig. 315.—Segments of tapeworms. To show characteristic branching of uterus, as seen in mature segments.

A, *Tænia solium*. B, *Tænia saginata*. ut., Uterus; g.o., genital opening.

(After R. Blanchard, in Brumpt's "Précis de Parasitologie.")

still found in England, is universal in Abyssinia, where multiple infections are common. It lives coiled up in the small intestine and may live as long as 35 years. One woman passed segments continuously for 15 years (Black, 1955).

Characters.—*T. saginata* is whitish and semi-transparent, measuring 4–10 m.; when fully adult it may contain 2,000 segments. The scolex is pear-shaped, cubical; 1–2 mm. in diameter with four lateral suckers but no rostellum or hooks. The suckers and sucker-like organ at the apex are frequently pigmented. (Fig. 314, 4.) The neck is long and half the width of the scolex. The older proglottides are elongated; gravid individuals are three to four times longer than they are broad. The genital pore is single, marginally placed at the hinder end of the proglottis, alternating regularly between the right and left margins. There are 20–35 lateral branches on each side of the uterus which may ramify. (Fig. 314, B.) The genital organs in the mature proglottis differ from those of *T. solium* in having about twice the number of testes (300–400) and in lacking the accessory ovarian lobe. Each gravid segment contains about 97,000 eggs and there may be 1,000–2,000 of them. The total output per year is reckoned at 594 million.

The egg is globular, 30–40 μ by 20–30 μ , with a double-shelled striated embryophore, which contains the onchosphere (Plate XXVII, 17). It is indistinguishable from that of *T. solium*.

Life-history.—Gravid proglottides emerge in faeces or pass to the exterior independently; they then creep into grass or herbage, where they disintegrate. When the eggs are eaten by the ox, the onchospheres are set free and pass into the small intestine, where they bore through the wall, and are carried to the muscles, especially the pterygoids and the fatty tissues round heart, diaphragm and tongue. Then cysticerci (*Cysticercus bovis*) are formed, measuring 7·5–9 mm. by 5·5 mm. They live for eight months in the ox and develop further in man, who constitutes the normal definitive host. The bladder is digested, and the liberated scolex, passing to the small intestine, affixes itself by suckers to the gut-wall. The cysts die at 48° C. Infected meat is known to inspectors as “measly beef.” In Egypt and Morocco the camel is the most important intermediary host. (Several varieties are described: *T. africana*, *hominis*, *philippina*, *bremneri* and *confusa*, have been attributed to new species, but are probably aberrant forms of *T. saginata*. Abnormal forms are common, such as *T. lophosoma*.)

Pathogenesis.—This worm occasionally causes abdominal pain, discomfort and anæmia. (For treatment, see p. 801.) Because of its large size the worm may be responsible for considerable disturbance in the normal functions of the digestive tract. The mass of an average specimen is about that of a liquid quart.

LARVAL FORMS OF TÆNIA IN MAN

The hydatid is the larva of *Echinococcus granulosus*; the adult lives in the intestine of dogs.

Cysticercus cellulosæ is the larva of *T. solium* (q.v.).

Cysticercus bovis is the larva of *T. saginata* and has been reported in man on a few occasions.

Cœnurus cerebralis is the larval form of *Tænia (Multiceps) multiceps* in the sheep. It is the size of a golf ball, and is diagnosed by percussing the sheep's head. The adult lives in the intestine of dogs, but is rare in man. The fourth case in man in S. Africa is described by Becker and Jacobson (1951). These cysts are far more common in sheep-rearing countries than has been realized. The focal symptoms are fainting attacks, hyperkinesia of the left arm and leg and staggering, but when the cysts discharge their contents they produce the psychological picture of toxic psychosis. Eight cases of *C. cerebralis* have been found by

Fain in Ruanda-Urundi and the Belgian Congo. They are suspected of being the larval stages of *Taenia brauni*, widespread in dogs of the E. Congo. *C. brauni* differs in the shape of the hooks which are larger in the former species and the guard is not so bilobed as in the latter.

Ventriculography shows dilatation of the lateral ventricles. Headaches are common and there is severe papilloedema. The hydatid complement-fixation test is positive. Two infections of the spinal cord causing spastic paraplegia have been reported by Cruszi and Landells.

In *M. multiceps* the rostellum measures 200–250 μ ; the number of hooklets is 24–32; the size of the large hooklets 134–185 μ and that of the smaller ones 70–130 μ . *M. glomeratus* is normally found in gerbilles and has been found in the chest wall of a negro in North Nigeria. Its hooks and scoleces are distinctive.



Fig. 316.—*Echinococcus granulosus*. $\times 15$. (After Leuckart, in Brumpt's "Précis de Parasitologie.")

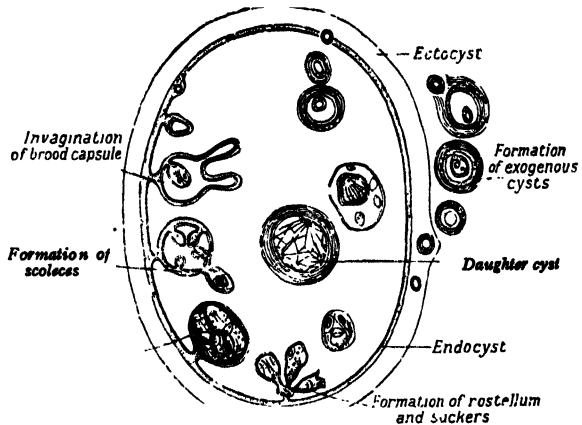


Fig. 317.—Schema of hydatid cyst. (After Blanchard.)

Genus: *Echinococcus*

ECHINOCOCCUS GRANULOSUS (Batsch, 1786) and *E. MULTILOCULARIS* (VOGEL)

Synonym.—*Taenia echinococcus*, or Hydatid.

Distribution.—The adult is a parasite of the dog, wolf, jackal, fox, arctic fox, monkey, kangaroo and in N. America the moose (*Alces americana*). It is common in Iceland, in the Esquimos, Australia, especially Victoria and Tasmania, New Zealand, and also in Arabia, Algeria, Tunis, Egypt, Abyssinia, Cape, Argentine and Uruguay, where the incidence in peons may be as high as 50 per cent. In Iceland 16.6–33 per cent. of humans are infected and 28 per cent. of dogs harbour the adult worm. After ingestion of the egg by the intermediate mammal (sheep, ox, pig, camel, man) hydatids form, especially in the liver.

Characters.—*E. granulosus* is very small, 3–5 mm. long, with a pyriform scolex, 0.3 mm. in diameter, provided at the apex with a projecting rostellum, four suckers and two circular rows of hooks, varying in size and number. (Fig. 316.) The neck is short and thick; the proglottides usually four in number. The last one is the longest (2–3 mm.); only one is sexually mature and this contains up to 5,000 eggs. The genital apertures are marginal, one to each proglottis, in an alternating arrangement. The testes are spherical and numerous. The

cirrus pouch is large and pear-shaped. The uterus is tubular and median, with short unbranched lateral diverticula. The adult is difficult to remove from the small intestine of the dog without breaking its head. Eggs appear in the dog's faeces. Sometimes the fourth segment also comes away. Man is probably not a suitable intermediary.

The egg is spherical, $32-38\ \mu$ by $21-30\ \mu$, and is double-shelled, the inner shell being thick. The egg is so similar to those of other tapeworms that it cannot be distinguished from them or from *Multiceps*. The onchosphere contains three pairs of embryonal hooklets. When swallowed, the shell is digested and the onchosphere escapes. After eight hours embryos can be found in the portal vein and liver, whence they are filtered out. The next filter is the lung, where a smaller number lodge. In three weeks the larval worm becomes vesicular and visible to the naked eye; in three months it attains a diameter of 5 cm. and within five weeks has doubled that size. The hydatid cyst wall is composed of a fibrous laminated layer formed by the host, a thick median striated layer secreted by the cyst, and an inner "germinal" layer from which the brood capsules and daughter cysts arise. There are two types of proliferation: (1) endogenous, (2) exogenous. In the former, proliferation is inwards towards the cyst cavity; in the latter it is outwards. The varieties of hyatid are so striking that *alveolar hydatid* (*E. multilocularis*) has now been recognized as a distinct entity which has a limited geographical distribution.

The brood capsules are formed from small nuclear masses of the parenchymatous germinal layer; later, they become vacuolated to form vesicles. Larval scoleces arise from a local thickening of the wall of the brood-capsule; the wall evaginates to form a protective cup for the growing scolex. Near the head-end the cuticle thickens and a circle of hooklets develops. The contractile part of the body of the scolex is capable of invaginating the head, so that in the typical resting position the scolex has the hooklets inside (Fig. 317). Free brood-capsules and free scoleces in the hydatid cyst cavity are known as "hydatid sand." In other cysts the brood capsules never produce scoleces and are known as *acephalocysts*.

Daughter-cysts may be produced by injury or by mechanical interference with the mother-cyst, inside which they arise from the detached germinal layer, and also from the brood-capsule cells; rarely by vesicular changes from the detached scoleces. In the liver the daughter-cysts are bile-stained. Intramuscular injection of scoleces causes formation of new cysts (Dévé and Dew) and this accounts for the dissemination of hydatid cysts throughout the body which sometimes occurs after operation.

Exogenous daughter-cysts in the omentum and bones are secondary, caused by herniation, or rupture of both germinal and laminated layers through weakened parts of the adventitia from intracystic pressure. By final exclusion of these herniations new cysts form.

Multilocular cysts occur in the lungs, and form solid tumours like sponges. They are produced by a double process: peripheral infiltration by the parasitic elements and central necrosis of the mass. Metastatic lesions are constant. Surgical treatment is almost impossible, though partial hepatectomy has been attempted (Brins). Rausch and Schiller (1956) have separated the Siberian and Behring Sea form as *E. sibiricensis* of which the adult stage occurs in the arctic fox and the chief intermediary is the tundra vole (*Microtus oeconomus*). It is specially common on St. Lawrence Island.

Dogs, foxes and jackals become infected by the adult worm through eating the organs, especially the offal, of sheep; the hydatid cyst wall is then digested and young tapeworms escape into the small intestine. Other naturally-infected animals are horse, camel, goat, monkeys, the Indian elephant, wild sheep, some

antelopes, moose, tapir, zebra, kangaroo, mongoose, cat, leopard, squirrel, rabbit. Man is infected by close association with dog—eating from the same dish or kissing. The eggs are also disseminated by house-flies. Hydatids are common in children under ten. The symptoms vary according to the site of the cyst, and include toxæmia, pyrexia, urticaria and multiple cutaneous eruptions. Tumours form in the liver and burst, disseminating secondary cysts in other organs, and these may suppurate and cause general peritonitis. In the brain the hydatid causes a cerebral tumour; in the liver, spleen and peritoneum it simulates malignant growth. In the lung it causes compression, and in the pleural cavity fluid exudate. In the kidney the mass resembles a hydronephrosis. It is also sometimes seen in the long bones, heart and orbit. By their destructive extension spontaneous fractures or compression fractures of vertebrae are produced. The relative frequency of cysts in various organs of man is: liver, 57–76 per cent.; lungs, 3·8–14 per cent.; omentum, mesentery and peritoneum, 1·37–18·2 per cent.; pleura, 0·7–0·9 per cent.; skin, subcutaneous tissues and musculature, 0·7–9·1 per cent.; spleen, 1·2–9·1 per cent.; brain, 0·9–2 per cent.; spinal cord, 0·8–0·9 per cent.; kidneys, 1·6–6·1 per cent.; bone, 0·8–9·1 per cent.

The cyst wall shows an outer laminated chitinous layer and an inner germinal layer of small cells with muscular fibres, calcareous bodies and glycogen. The cyst consists of a clear, watery fluid of specific gravity 1007–1015, containing albumin and a protein allied to casein, sodium chloride (0·5 per cent.), phosphates and sulphates of soda, sodium and calcium, succinates, traces of sugar and inositol, and an intracystic toxin allied to albumin. Hydatid fluid in the abdominal cavity produces shock, which is probably anaphylactic, and the escaped daughter cysts produce others. The largest hydatid cyst ever found was in a man in Australia and it contained 50 quarts of fluid. Others have been found to contain 10 to 15 quarts. In a woman in Iceland, one measuring 20 in. in diameter and containing $3\frac{1}{2}$ gallons of fluid, was removed. Hydatids are usually slow-growing, and cysts may be sterile. In man they tend to die and calcify, but may suppurate. Surgeons in Uruguay aspirate the fluid contents of the cyst. Following incision into the cyst itself the wall of the cyst is scraped out and the remaining parasitic tissues treated with 1 per cent. formalin. Then the cavity is washed out with physiological saline, thus leaving no appreciable amount of formalin.

ALVEOLAR HYDATID (*Echinococcus multilocularis*) Vogel

This new species is the cause of the alveolar hydatid which for so long has been the object of discussion. It has a restricted geographical distribution in E. Germany, Alps, Jura and Russia. The final hosts are foxes, dogs, cats and the natural intermediate hosts, field mice, rodents and, occasionally, man. In islands of the Behring Sea the final hosts are sledge dogs and arctic foxes. The alveolar larval phases are found in the livers of burrowing mice.

E. multilocularis differs in that herbivora play no part in its life-history. Field mice take up its eggs from foxes and the "larval stages" develop in the livers of mice and then foxes eat them. Sporadic infections of man can occur during skinning of foxes. It is also conveyed by dirty hands in collecting strawberries, bilberries and whortleberries.

In the adult worm the differences are: the position of the genital pore in front of the middle of the proglottis. The number of testes is 21–29 (as against 45–65). These lie behind the posterior end of the proglottis in the region of the cirrus sac. The uterus has no lateral branches. The length of the mature worm is 1·4–3·4 mm. (as against 5–8 mm.).

Diagnosis.—The hydatid appears as a cystic swelling which, if near the surface, produces fluctuation, "hydatid thrill"; if punctured by a syringe the scoleces

and hooks are recognized. X-rays are helpful in hydatid cysts of lung, liver and when the long bones are involved. There are other aids to diagnosis. (1) The precipitin test (Welch and Chapman):—equal parts of hydatid fluid and serum are mingled and incubated at 37° C.; if the fluid is infected a precipitate forms. (2) The complement-deviation reaction (Weinberg and Parvu) is generally accepted as reliable. It is performed by the Wassermann technique. Hydatid fluid (0.4 ml.) is mixed with an antigen made of scoleces macerated with alcohol (Fairley). (3) The Casoni, or intradermal, test is diagnostic in 90 per cent. (Kellaway and Dew). A few drops of the hydatid of a sheep are injected intradermally, and a reaction appears in ten minutes as a large wheal surrounded by erythema. It fades in an hour. A secondary reaction appears eight hours later; it is large and infiltrated by cedema. This test remains positive for years after the surgical removal of hydatid cysts.

Prophylaxis.—In endemic areas periodic deworming of dogs is effected by arecoline hydrobromide in the dosage of 4 mgm. per 100 pounds. The dogs are tied up for 4 hours after treatment and all faeces collected and burned. Refuse from slaughter houses must be made inaccessible to dogs.

Genus: *Hymenolepis*

HYMENOLEPIS NANA (Siebold, 1852) (Fig. 318).

Synonym.—*Tænia nana*, *H. murina*, "Dwarf Tapeworm."

Distribution.—It is found in warm countries, Egypt, Sudan, Siam, India, Japan, South America (Brazil, Argentine, and especially Cuba), South Europe (Portugal, Spain and Sicily, where it affects 10 per cent. of the children). It lives in the small intestine (Grassi believed it to be identical with *H. fraterna* of the rat) and parasitizes the Syrian hamster (*Cricetus auratus*) (Watson) (Fig. 318).

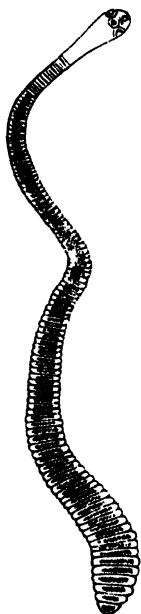


Fig. 318.
Hymenolepis nana.
Magnified.

Characters.—*H. nana* is 25–45 mm. long by 0.5–0.9 mm. and has 100–200 proglottides. The scolex measures 139–480 μ , is sub-globular with a well-developed rostellum, a single crown with 20–30 hooklets (14–18 μ), and four globular suckers (80–150 μ) (Fig. 314, 1). The neck is long, the proglottides short anteriorly, but the posterior ones increase in size and are broader than they are long. The genital pores are marginal and placed near the anterior border. There are three testes. The vas deferens widens into the seminal vesicle, and the gravid uterus occupies an entire segment.

The egg is oval and globular, and there are 8–180 in each segment. It has two membranes, outer (vitelline), 40–60 μ , and inner, 20–30 μ (Plate XXVII, 20). There is a conspicuous mammillate projection at each pole, enclosing an onchosphere with three pairs of hooklets.

The segments, when freed, are partially digested and the eggs, set free in the faeces, are easily detected.

Life-history.—This worm forms an exception to other members of the group, in that it has no intermediate host: the larva enters the villus of the intestine to become a *cercocystis* (Villot). In 40–70 hours after ingestion the scolex appears; in 80–90 hours the rostellum has hooklets and then passes into the lumen of the intestine attached to the epithelium of the villus by a short neck. The rapidity of development varies greatly. Strobilization is rapid; the proglottides mature in ten to twelve days, and after thirty days eggs appear in the

fæces. *H. fraterna* of the rat is morphologically identical, but its intermediary hosts are fleas and beetles.

Pathogenesis and treatment.—*H. nana* appears in large numbers—hundreds or thousands. It may produce no symptoms, but occasionally there is abdominal pain and diarrhoea, rarely epileptiform convulsions, headache or strabismus. Nervous phenomena are due to the toxic products of the parasite. On account of its minute size, this worm is often overlooked. Diagnosis is made by finding the eggs in the fæces; care is needed because they are so transparent that they may be missed.

H. nana is not easy to dislodge by filix mas or oil of chenopodium; tetrachlorethylene (p. 881) is said to be more effective. Chloroquine and Acranil (see p. 866) have been recommended. Gentian violet is considered valuable, given in hard gelatin capsules; for an adult, gr. 1 three times daily for varying periods. One month should elapse before cure is assumed. The stools should then be examined by the D.F.C. method (p. 1101). An infected patient should not sleep in the same bed with another person.

HYMENOLEPIS DIMINUTA (Rudolphi, 1819)

Distribution.—This is a parasite of rats (*Rattus decumanus*, *R. alexandrinus*) and mice (*Mus musculus* and *M. sylvaticus*); it is found in man in Italy, South America, the Congo (common: Chesterman) and West Indies.

Characters.—It measures 20–60 cm. by 3·5 mm. The head is small and cuboidal with a small infundibulum. At the apex is a rudimentary rostellum with four small, unarmed suckers. The neck is shorter than the head. The proglottides increase in size as the tail is approached, and are broader than they are long.

The egg is circular or ovoid, measuring 60–80 μ . Its outer shell is yellowish and thickened, with indistinct radiations, and contains a hexacanth onchosphere.

Life-history.—The cysticercus stages occur in the body cavity of insects and fleas during their larval stages: *Nosopsyllus* (*Ceratophyllus*) *fasciatus*, *Xenopsylla cheopis*, *Leptosylla segnis* (mouse flea); *Pulex irritans*; in coleoptera and lepidoptera such as *Asopia farinalis*, *Anisobasis annulipes*, *Akis spinosa* and *Scaurus striatus*; also in South America, in *Dermestes vulpinus*, *D. peruvianus*, *Ulosonia parvicornis* and *Embia argentina*.

The rat becomes parasitized by eating infected fleas or other insects. The cysticercoids, when ingested by the definitive host, become adult in 17 days.

Treatment.—*Oleoresin of aspidium* is the drug of choice (see p. 876).

Genus: *Dipylidium*

DIPYLIDIUM CANINUM (Linn., 1758)

Distribution.—This is a common parasite of the dog, cat and jackal. There are 100 records of its occurrence in man, especially in children in European countries.

Characters.—It lives in the small intestine, measuring 15–40 cm. by 2–3 mm. The scolex is small and globular, 0·55 mm. in diameter. The rostellum is retracted into the infundibulum and has three to four circles consisting of 28–30 hooklets (14–18 μ) of “rose-thorn” shape and four elliptical suckers (Fig. 314, 2). The proglottides are narrow and there are 200 or more of them. The segments (80–175 in number) measure 6–7 mm. by 2–3 mm. Two sets of genital apparatus are found in each segment; the genital pores are placed symmetrically at the lateral margins. The uterine cavities contain egg-nests, each consisting of 8–15 eggs. Mature proglottides leave the intestine. The egg is round, 35–40 μ across.

Life-history.—The cysticercoid stage is passed through in the dog-louse (*Trichodectes canis*), dogflea (*Ctenocephalides canis*), cat flea (*C. felis*), and human flea (*Pulex irritans*). Eggs are eaten by the larval flea, and the hexacanth embryo develops in the adipose tissue and muscles, being delayed until the adult stage is reached, first appearing as a proceroid and later as a cysticercoid larva. Infection of man is accidental, due to swallowing infected fleas.

Pathogenesis and treatment.—Usually there are no symptoms. Treatment is by filix mas, as for other forms of tænia.

Genus: *Raillietina*

R. CELEBENSIS, R. MADAGASCARIENSIS (formerly *Tænia madagascariensis*), R. QUITENSIS

These worms are found in Celebes, Siam, British Guiana, Mauritius and Formosa, and the last has been reported by Léon in Ecuador and also by Baer and Sanders in Australia and from *Rattus assimilis*. Two cases are now reported by Chandler from Siam as *R. sivoragi*. They are characterized by numerous hooklets of "coal-hammer" shape on the suckers and rostellum, and by unilateral genital pores on the proglottides. Ripe segments contain egg capsules. The ovoidal eggs possess conspicuously large hooklets. Usually they are parasites of birds, more rarely of rats. Their intermediary hosts are probably flies.

Genus: *Inermicapsifer*

This genus closely resembles the foregoing and cannot be distinguished from it by the ripe proglottides, but the head and the suckers are unarmed. *I. arvicanthidis*, a parasite normally of the field rat, was found by the Editor in a European child from Kenya; since then others have been reported by Fain in Ruanda Urundi and Baer in Arusha, Tanganyika. It is suggested that it is commoner than has been supposed. No less than 12 species of *Inermicapsifer* are parasites of hyraxes and rodents in Africa. *I. cubensis* appears to be common in Cuba where 76 cases in man have been described by Kouri. Fain (1956) has shown that it is identical with the foregoing.

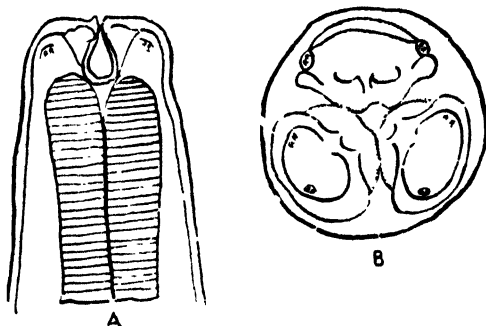


Fig. 319.—Head of *Ascaris lumbricoides*; (A) ventral view; (B) anterior view, showing oral labia. (After Faust.)

PHYLUM NEMATOMORPHA

Class: Nematoda or Roundworms

The sexes of these worms are separate. They are cylindrical, non-segmented and taper at both ends. They are white or yellow, sometimes semi-transparent and their eggs are characteristic (Plate XXVII).

Superfamily: Ascaroidea

Genus: *Ascaris*

ASCARIS LUMBRICOIDES (Linn., 1758)—“Round Worm”

Distribution.—World-wide.

Characters.—*A. suilla* of the pig is indistinguishable from *A. lumbricoides* whilst allied species are found in the cat, dog and horse. The worm inhabits the small intestine. The female measures 20–35 cm. by 3–6 mm.; the male 15–31 cm. by 2–4 mm. Both are pale yellow or brown, with whitish longitudinal lines, round, tapering at both ends. The mouth is at the anterior end, guarded by thin lips with finely denticulated margins (Fig. 319). The anus is subterminal. In the female there are paired genital tubes, containing the uterus, *receptaculum seminis*, oviduct and ovary. Tubules and ducts attain a length of 12 cm. The total capacity of the genital tubules at one time has been estimated at 27 million eggs; the average day output is 200,000. The male has the tail curved into a semi-circle and has two rows of tactile papillæ and two chitinous spicules. The life span is about 10–12 months.

The egg (Plate XXVII, 7, 8, 9, 10) measures 50–70 μ by 40–50 μ and is elliptical, encased in a rough albuminous coat giving it a mamillated appearance. It is usually stained by faecal pigments.

Life-history.—When the eggs are passed in the faeces, there is no segmentation or differentiated embryo. In water, or in moist earth, at 36–40° C. within two to four months the embryo is seen coiled up and moving inside the egg-shell. The

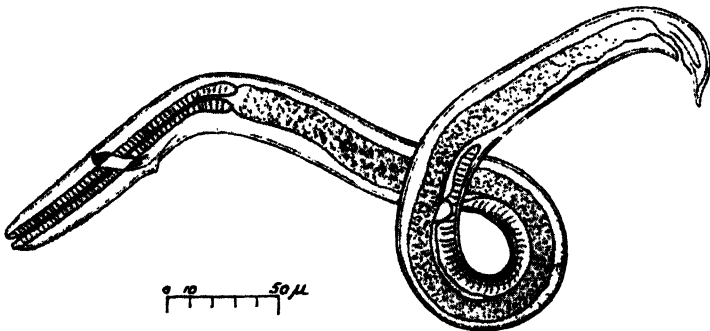


Fig. 320.—Larva of *Ascaris lumbricoides* recovered from the trachea of a rat eight days after ingestion of eggs. (After Brumpt's "Précis de Parasitologie.")

larva undergoes a moult before hatching and must be transformed into a second-stage larva of the “rhabditoid” type before it is infective. The embryo does not emerge from the egg until it is swallowed. The egg-shell is then softened by the gastric juice and hatches in the small intestine. The rhabditiform larva penetrates the mucous membrane, enters the blood *via* the heart and lungs, and reaches the alveolar capillaries where it has a “blood bath.” As the larvæ cannot pass through they burrow through the wall of the alveolus and enter the respiratory tree, finally being carried up the trachea by ciliary action. Eventually, on reaching the vocal cords the majority of the larvæ are swallowed for the second time and reach the small intestine. The second invasion is often accompanied by severe allergic reactions, urticarial reactions and fall in blood pressure. The whole process occupies ten to fourteen days. During this time the larva moults

twice (once after five to six days and the second time after the tenth day). The larvæ measure 1.3–2 mm. on the tenth day (Fig. 320) and 1.75–2.37 mm. on the fifteenth (Stewart, Yoshida, Fülleborn, Brumpt, Mosler and Lutz). Larvæ may reach the intestine as early as the fifth day. The fourth ecdysis takes place in the intestine between the twenty-fifth and twenty-ninth days. In man the incubation period (to time of first oviposition) occupies a period of 60–75 days. The diameter of the migrating larvæ from the pulmonary capillaries to the terminal air spaces is considerably larger than that of the capillaries. Porcine ascaris larvæ are unable to complete their development in man: human ascaris behave similarly in the pig.

In the lungs the larvæ cause damage, hæmorrhage and toxic absorption. Eosinophil cells are found in the alveoli. The larvæ grow ten times longer whilst migrating through the lungs and feeding on the blood during a period of ten to twelve days. A clinical syndrome closely resembling "tropical eosinophilia" is sometimes produced and in sections of the lung larval ascarides have been demonstrated by Danaraj in Singapore. Aberrant migrations to thyroid, thymus and spleen, occasionally to the brain and spinal cord, have been observed. Respiratory symptoms are noted 26 hours to four or five days after ingestion of eggs, and present the clinical picture of lobar pneumonia (ascaris pneumonia). The adult worm may give rise during its wanderings to symptoms such as intestinal obstruction, general peritonitis, extraperitoneal abscess and even asphyxiation, when in the trachea. Liver abscesses due to migrating ascarides in children are quite common in Singapore. The use of carbon tetrachloride has been shown to be responsible for aberrant migrations of these worms. Exceptionally, viable eggs have been found in tubercle-like lesions in the mesentery. Heavy infections in children (500–1,500 worms) may cause intestinal obstruction and perforation. Children are occasionally infected by the ascaris of the cat and dog, *Toxocara canis* and *T. cati*. (For treatment, see p. 788).

Genus: *Lagochilascaris*

Lagochilascaris minor Leiper, 1909

Lagochilascaris minor which resembles a small ascaris and is normally found in the intestine of the cloudy leopard (*Felis nebulosa*) is quite common in Surinam and in the Caribbean. It has been found in tonsillar and mastoid abscesses, while Winkel and Treurniet (1956), in Surinam, removed hundreds from a swelling in the neck and ramifying loculi.

The adult worm is recognized by a longitudinal furrow with indentations. The hare-lip-like parts of the mouth have given the worm its name. The eggs which occur in profusion resemble small ascaris ova. The male is 9 mm. \times 0.4 mm.: the female 15 mm. \times 0.5 mm. Both have a triangular keel-like cuticular ledge along the entire extent of the lateral line.

Superfamily: Spiruroidea

Genus: *Gnathostoma*

Gnathostoma spinigerum Owen, 1836

This worm is found commonly in the stomach of the tiger, dog, wild cat and leopard. It was first found in man in 1890 by Levensen in a breast abscess in a woman from Siam: subsequently a second occurrence was reported by Leiper in 1909. Additional human cases have occurred in Malaya, Japan and China. The adult worms are 11 to 25 mm. for males and 25–54 mm. for females. They are reddish in colour and slightly transparent with a globular cephalic swelling, separated off from the rest of the body by a cervical constriction.

The anterior half of the cuticula is provided with leaf-like spines. The posterior part of the body is smooth. The eggs are transparent, oval and measure

65–70 $\mu \times$ 38–40 μ and, when oviposited, are in the morula and gastrula stages. The entire life-cycle is still obscure, though the larval stage has been found by Kitamura (1952) in fishes (*Ophicephalus argus*, *O. tadianus*) in the Yangtse Valley, China. Wandering larvæ in the human host produce a creeping eruption—*larva migrans* (p. 836).

Genus: *Physaloptera*

PHYSALOPTERA CAUCASICA (v. Linstow, 1902)

Synonym.—*P. mordens* (Leiper, 1907).

Distribution.—Normal hosts are monkeys. In man it has been found in Central Africa, Portuguese East Africa, Uganda and Nyasaland. It lives in the œsophagus, stomach, small intestine, and occasionally in the liver.

Characters.—The female (2.4–10 cm. by 1.14–2.8 mm.) has a posterior end tapering to a sharp point, two ovaries, a single uterine tube, and a vulva in the anterior part of the body. The male (1.4–5 cm. by 0.7–1 mm.) has two lateral alæ on the tail, formed by expansion of the cuticle, four pairs of pedunculated papillæ—six pairs sessile—one unpaired postanal papilla, and two spicules of unequal length. In both sexes the mouth is guarded by two large lips, armed with two papillæ and rows of teeth, which serve to grip the mucous membrane. (Fig. 321.)

The egg (45 μ by 35 μ) has a double-contour, smooth, thick, colourless shell.

Life-history.—The life cycle is unknown; insects possibly act as intermediaries. The clinical symptoms are indeterminate. The worms live with heads embedded in the digestive tract from the œsophagus to the ileum.



Fig. 321.—Head of *Physaloptera caucasica*. (After Leiper.)

Genus: *Gonglyonema*

Gonglyonema pulchrum Molin, 1857

This is a spirurate nematode of a genus in which there are six species. It is a rare infection in man and pig, but all ruminants are optimum hosts.

The worm lives most commonly in the upper portion of the digestive tract, where it forms sinuous galleries in the mucous membrane and subdermal connective tissues. The colour is white. The male is 62 \times 0.15–0.3 mm.: the female is 145 \times 0.2–0.5 mm. The anterior extremity is covered with a variable number of bosses or scutes arranged in eight longitudinal series.

The transparent thick-shelled oval eggs are embryonated when laid and are 50–70 μ in length by 25–37 μ . Development takes place in dung beetles of genera *Apodius* and *Onthophagus*, as well as in a small cockroach. About nine human cases are recorded in tongue, mouth and œsophagus, mostly in southern U.S.A. The last record is from a negress in S. Carolina by Young (1953).

Superfamily: Strongyloidea

Genus: *Ancylostoma*

ANCYLOSTOMA DUODENALE (Dubini, 1843) (Fig. 322)

“Old-World Hookworm,” “Miner’s Worm”

Distribution.—This worm was originally confined to Europe, but is now known in America, Asia, even Germany and England—wherever humidity and temperature are suitable (e.g., the Simplon tunnel, and the tin mines of Cornwall). It is very common in Egypt. It requires a temperature of 75° F. for development outside the body; this constitutes a limiting factor in distribution.

Characters.—Both sexes are cylindrical, white, grey, or reddish brown (from ingested blood). The female (1–1.3 cm. by 0.6 mm.) (Fig. 322), is cylindrical and slightly expanded posteriorly. The vagina is in the posterior third. The body cavity is occupied by the ovary and coiled uterine tubes packed with eggs.

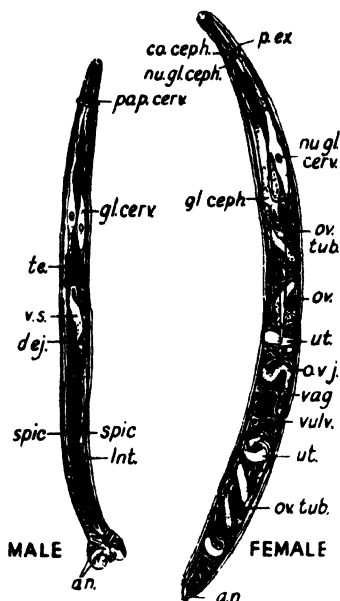


Fig. 322.—*Ancylostoma duodenale*, male and female. $\times 14$. (After Looss.)
(For actual size, see Fig. 325, p. 791.)

An., anus; co.ceph., cephalic nerve commissure; d.ej., ejaculatory duct; gl.cerv., cervical gland; int., intestine; nu.gl.cerv., nucleus of cervical gland; ov., ovary; ov.tub., ovarian tubules; oej., ojector; p.ex., excretory pore; pap.cerv., cervical papilla; spic., spicules; ta., testes; ut., uterus; vag., vagina; v.s., vesicula seminalis; vulv., vaginal opening.

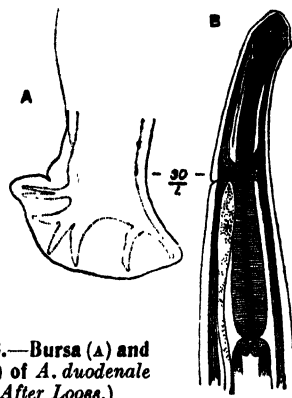


Fig. 323.—Bursa (A) and head (B) of *A. duodenale* δ (After Looss.)

The maximum egg-output occurs fifteen to eighteen months after infection. The male (0.8–1.1 cm. by 0.4–0.5 mm.) has a copulatory bursa consisting of an

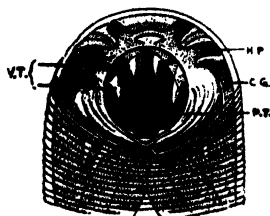


Fig. 324.—Head of *A. duodenale*, showing hook-like ventral teeth. $\times 50$. (After Looss.)

C.G., Cephalic gland; H.P., head papillae; P.T., pharyngeal teeth; V.T., ventral teeth.

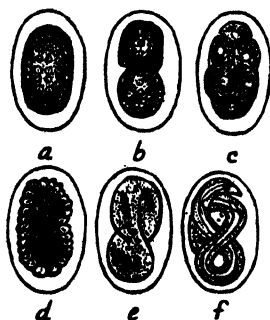


Fig. 325.—Developmental stages of the larva in eggs of *A. duodenale*. (a), (b) and (c) are seen in fresh stools; (d), (e) and (f) when the stool is stale. $\times 300$. (After Looss.)

umbrella-like expansion of the cuticle; the dorsal ray is divided towards the distal end into smaller rays, which again divide into three unequal portions

(Fig. 323). There are two long delicate spicules. The genital papillae are tactile, finger-like projections near the ano-genital opening. Owing to the situation of the genital openings in both sexes the worms in copulation assume a Y-shaped figure.

Two well-marked cephalic glands occupy the anterior third in both sexes and secrete an anticoagulating ferment. The mouth end is bent dorsally. The excretory pore is ventral, placed at the level of the oesophagus. The buccal capsule is lined with chitin, and contains two pairs of sharp teeth on its ventral aspect (Fig. 324). The worm lives mostly in the jejunum, and to a lesser extent in the duodenum, but not in the ileum.

At autopsy 500-1,000 or more worms may be found. They have a life-span of four to seven years. The interval between active infection and final disappearance of eggs in the faeces may be 76 months. The female produces 25-35,000 eggs a day and during its lifetime 18-54 million.

The egg ($60\ \mu$ by $40\ \mu$) (Fig. 325) is elliptical, with a transparent shell. When fresh-laid, it contains 2-4 blastomeres (Plate XXVIII, 14). The life history is given on p. 985.

Pathogenesis and treatment.—See pp. 796-798.

ANCYLOSTOMA BRAZILIENSE (Gomez, 1910)

Distribution.—It is found in dogs and cats in Brazil. In Ceylon it was described as *A. ceylanicum* from the civet cat.

Characters.—It is rarely found in the small intestine. Usually it is part of a mixed hookworm infection in man in India, Malaya, and Siam. It is smaller than *A. duodenale* and the internal pair of ventral teeth are smaller than the corresponding teeth of that species. The female is 1 cm. long and the male 8.5 mm. The rays in the copulatory bursa differ (Fig. 326) from those of *A. duodenale*, and are distinctive.

The egg is indistinguishable from that of *A. duodenale*.

Life-history.—This is the same as *A. duodenale*. Man is apparently an unsuitable host. The larva does not penetrate into the blood stream easily, but wanders under the skin, causing irritation ("larva migrans," p. 836), especially in South United States (Kirby-Smith, Dove and White, 1925-8).

Pathogenesis.—The signs and symptoms resemble those of *A. duodenale*.

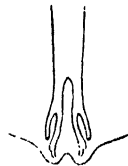


Fig. 326.—Dorsal ray of *Ancylostoma braziliense*. (After Leiper.)

Genus: *Necator*

NECATOR AMERICANUS (Stiles, 1902) (Fig. 327)

"New-World Hookworm"

Distribution.—This is the only species of the genus. It is found in America, and is also common in West Africa, Ceylon, India, Pacific Islands, Malaya, the Philippines, and in pygmies from the Ituri Forest. Ninety per cent. of all hookworms from the tropics are of this species. It was probably introduced to America by slaves from Africa.

Characters.—It is found in the small intestine of man, and also of the gorilla, patas monkey, rhinoceros, pangolin and a rodent (*Cændu villosus*). On the

whole, *N. americanus* is a shorter and more slender worm than *A. duodenale*. The female (0.9–1.1 cm. by 0.4 mm.) has the vulva placed slightly in front of the middle of the body, so that it copulates at a Y-shaped angle, as in *A. duodenale*. The male (7–9 mm. by 0.3 mm.) has the copulatory bursa closed and blunt, and a short dorso-median lobe which appears as if divided. (Fig. 327.) The dorsal ray branches at the base into divergent arms with bipartite tips (tridigitate in *A. duodenale*). The base of the dorsal and dorso-lateral rays is short (Fig. 328). Two separate spicules unite to form a single terminal “fish-hook” barb. The living worms are greyish-yellow, at times reddish.

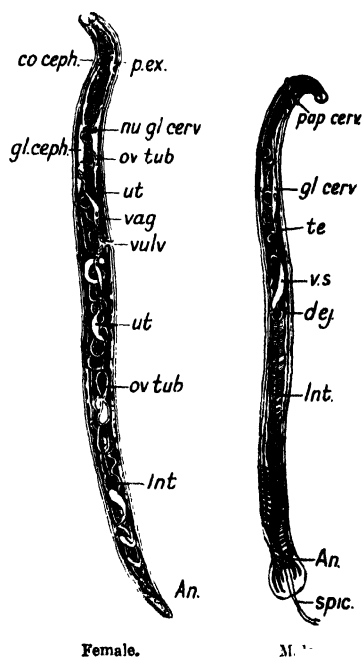


Fig. 327.—*Necator americanus*.
For legend see Fig. 322.

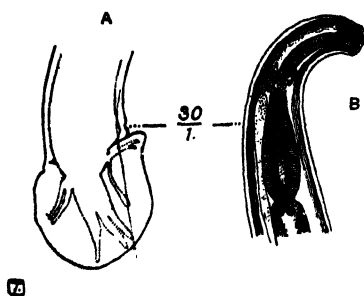


Fig. 328.—Bursa (A) and head (B) of *N. americanus*. (After Looss.)

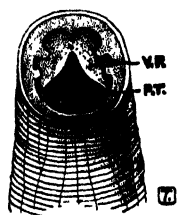


Fig. 329.—Head of *Necator americanus*, showing pharyngeal teeth (p.t.) and ventral plates (v.p.). $\times 50$.

The sudden dorsal bend of the head, especially in the female, is distinctive. The buccal capsule is smaller than in *A. duodenale*, with an irregular border. In place of four hook-like teeth there is a ventral pair of cutting plates (Fig. 329). The first pair of dorsal teeth are represented by chitinous plates. The outlet of the dorsal gland constitutes a “dorsal rib” or tooth which projects into the oral cavity. Deeply placed in the capsule are one pair of dorsal and one pair of sub-medial lancets.

The egg is slightly larger than that of *A. duodenale* (64–75 μ by 36–40 μ), but otherwise similar. The infective larva can be differentiated from that of *S. stercoralis* by the larger buccal vestibule and the intervening space between the oesophagus and midgut. Forty-four eggs per grm. of faeces are reckoned to represent one female worm. The female lays from 6,000–20,000 eggs per day. The estimated duration of life is about 5 years.

Life-history.—This is identical with that of *A. duodenale*.

SUMMARY OF LIFE-HISTORY OF HOOKWORMS (Fig. 330)

The eggs are deposited in the lumen of the intestine with two, four, or eight blastomeres. They must have a supply of oxygen to develop.

(1) The embryo moves about inside the shell and alters its shape, then escapes and gives rise to:—

(2) The rhabditiform larva burrows into the faeces and feeds especially on bacteria. At first it has a double-bulbous œsophagus. (Fig. 330, b). Feeding voraciously, it stores oil globules in its intestinal wall. It moults on the third day; on the fifth the œsophageal bulb disappears, and the larva becomes elongated and fully developed at 20–30° C.; the larva on the 3rd day is 400 μ , and on the 5th it is 500–700 μ long. It then moves away from the faeces into the earth, moults again and becomes:—

(3) The infective filariform, or third stage larva, with a well-developed mouth capsule, a simple muscular œsophagus and protective sheath, the walls of which are seen as two bright lines in the living specimen. It moves towards the oxygen supply, but cannot swim in water. The larvæ are most numerous in the upper inch of the soil. They are capable of ascending 2–3 ft., but lateral movements are limited. Attracted by warmth, it is quiescent in the cold; it moves along a thin film of water as well as in the earth. Enabled by the sheath to withstand a certain degree of desiccation, it can live in warm damp soil under optimum conditions for two years. This is the infective stage. (Fig. 330, a.) Direct sunlight, drying or flooding or salt water are fatal. On penetrating the skin of the host, the sheath is left behind, and the larva then enters the lymphatics, gains the blood-stream, and reaches the lungs on the third day. If pyogenic

bacteria enter the skin with the larvæ an open lesion may develop, producing "ground itch." Breaking through the alveoli of the lungs, it enters the bronchioles, and travels *via* trachea and œsophagus to the stomach. During this migration the third moult takes place and the buccal capsule is formed. On arrival in the intestine on the seventh day it undergoes its fourth moult; the terminal buccal capsule is changed into the "provisional buccal capsule" with the mouth opening directed dorsally, as in the adult, but without teeth. On the fifteenth day the "provisional buccal capsule" is cast off, and it then assumes the adult form with adult buccal capsule and bursa in the male. In three to five weeks it becomes sexually mature, copulates and then produces fertile eggs. Females of *A. duodenale* lay about 2½ times as many eggs as do females of *Necator americanus*.

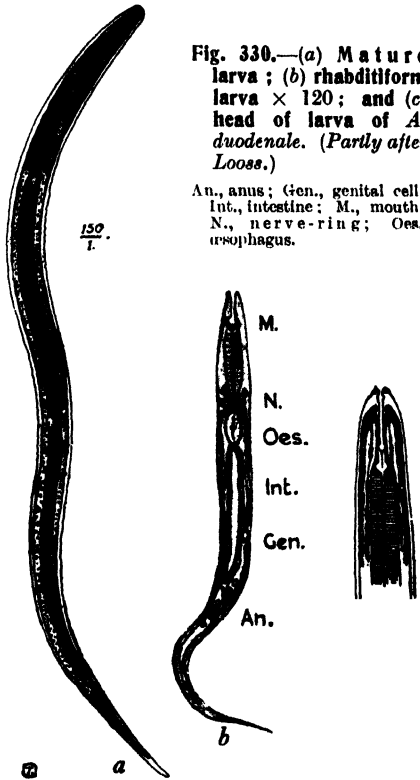


Fig. 330.—(a) Mature larva; (b) rhabditiform larva $\times 120$; and (c) head of larva of *A. duodenale*. (Partly after Looss.)

An., anus; Gen., genital cell; Int., intestine; M., mouth; N., nerve-ring; Oes., œsophagus.

Cultivation of hookworm larvæ.—A small portion of fæces is rubbed over a Petri dish with warm water, making a uniform layer like pea-soup. Inside the cover is placed a circle of wet blotting paper. This is kept moist and incubated at 75° F. under a shade. If there is too much water the eggs will not develop. The larvæ climb up the sides of the dish on to the blotting paper where they can be studied.

Differentiation of third-stage larvæ : Table XII

	Necator.	Ancylostoma.
Oral capsule	Sharply defined ; visible dorsally and ventrally	Hardly visible ; more marked dorsally than ventrally
Tail	Rather blunt	Pointed
Zone of closing cells	Leaves only small space between œsophagus and intestine	Leaves considerable space

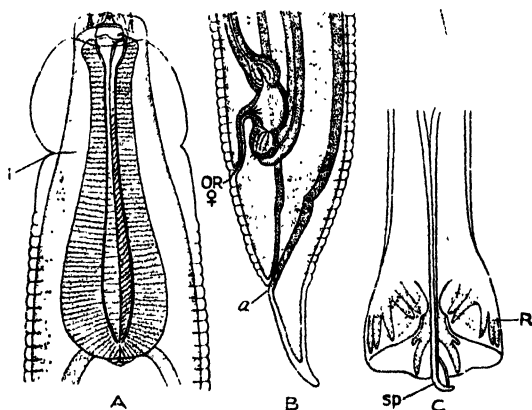


Fig. 331.—(*Aesophagostomum apiostomum* (brumpti). (Partly after Railliet and Henry).

A, Head, showing cuticular expansion and oral vestibule. B, Tail of female. C, Tail of male, showing copulatory bursa.
a., Anus; Cl., ventral cleft; OR., vaginal orifice; R., characteristic rays of bursa; Sp., spicule.

The striation of the sheath is indistinct in *A. duodenale*, but very distinct in *A. braziliense*. Rhabditiform ancylostome larvæ are similar to those of *S. stercoralis*, but are slightly more attenuated posteriorly and possess a much longer buccal vestibule. Infection (third stage) duodenale larvæ can also be differentiated from those of *necator* by the œsophageal shears which are unequal in thickness in *Ancylostoma* but equal in *Necator*.

Genus: *Aesophagostomum*

ÆSOPHAGOSTOMUM APIOSTOMUM (Willach, 1891) (Fig. 331)

Distribution.—This worm has been found in 4 per cent. of prisoners in the jails of North Nigeria. It is a common parasite of the cæcum and colon of old-world monkeys in Africa, the Philippines and China.

Characters.—When free or encysted under the mucous membrane of the large intestine it produces a condition like polyposis intestini.

The female (1 cm. by 0.325 mm.) terminates posteriorly in a sharp point and has a vulva in its anterior half. The male (0.8–1 cm. by 0.35 mm.) has a copulatory bursa with a dorsal ray bifurcating into branches and forming a horse-shoe-shaped structure, each limb giving off a short lateral horn near its base (Fig. 331, C).

The egg (60 μ by 40 μ) closely resembles that of *ancylostoma*, but is passed in an advanced stage of development.

Life-history.—The larvæ hatch from the eggs in the soil. When mature, they are unsheathed. The rhabditiform stage is swallowed, and passes through the stomach and intestine. Then it invades the wall of the cæcum where it forms nodules and, on occasions, it may penetrate the bowel and form intraperitoneal abscesses. The immature worms break out into the lumen, attach themselves to mucosa and become adult.

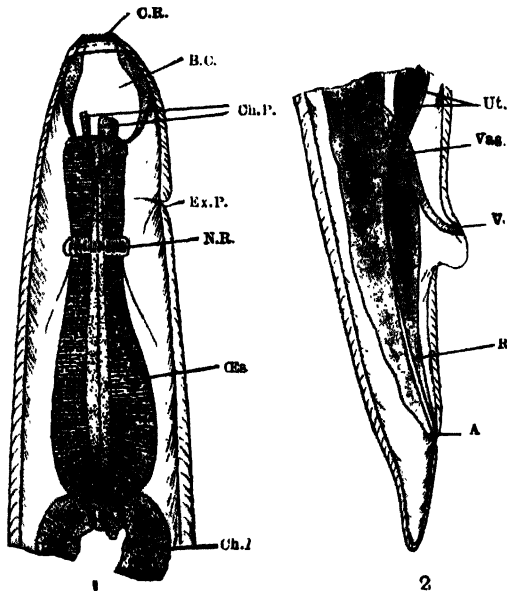


Fig. 332.—*Ternidens deminulus*, female. (After Leiper.)

1, Anterior extremity. 2, Posterior extremity. A., anus. B.C., buccal cavity. Ch.I., chyle intest. C.R., corona radiata. Ch.P., chitinous plates. N.R., nerve-ring. CEs., cesophagus. R., rectum. Ut., uterus. Vas., vagina. V., vaginal opening.

Pathogenesis and treatment.—This worm produces dysenteric symptoms. It is apparently susceptible to phenothiazine, 3–7 grm., and tetrachlorethylene (see p. 501).

ESOPHAGOSTOMUM STEPHANOSTOMUM var. *thomasi*
(Railliet and Henry, 1909)

Distribution.—This is a common parasite of monkeys (*Cercopithecus callitrichus*) and gorillas. The first case reported in man was in Brazil; the

patient died of dysenteric symptoms and peritonitis (Thomas, 1910). It has also been reported in French Guiana (Joyeux) and in North Nigeria (Johnson, 1934).

Characters.—The morphology resembles that of *O. apiostomum*, but both sexes are larger and is distinguished by a corona radiata with 38 leaf-like spines. The eggs in the faeces resemble those of ancylostoma.

Life-history.—This is probably similar to that of *O. apiostomum*.

Genus: *Ternidens*

TERNIDENS DEMINUTUS (Railliet and Henry, 1905) (Fig. 332)

Distribution.—This stronglylid nematode is relatively common in monkeys and baboons in Africa and Asia—*Macaca sinicus*, *M. cynomolgus*, *Cercopithecus pygerythrus* and *Papio porcarius*. In the small intestine of man it is not uncommonly found in Nyasaland, Portuguese East Africa, the Transvaal and Southern Rhodesia. It is not pathological, unless present in large numbers.

Characters.—The female (14–16 mm. by 0.73 mm.) has a genital orifice posterior and subterminal, and a short vagina opening into two uterine tubes. The male (9.5 mm. by 0.56 mm.) has the dorsal ray of the copulatory bursa dividing into two distal extremities, and each branch bifurcates again. (Fig. 333.)

The worm resembles a female ancylostome; its anterior extremity is not bent, and the mouth capsule is terminal, with a corona of setæ. At the base of the cup-like buccal capsule three serrated teeth guard the entrance to the œsophagus; this is characteristic of the genus *Ternidens*. (Fig. 332.)



Fig. 333.—Bursa of *Ternidens deminutus*, ♂. (After Brumpt.)



Fig. 334.—Egg of *Ternidens deminutus*. (After Blackie.)

The egg (84 μ by 40 μ) is delicate, transparent, and in an advanced stage of segmentation resembles that of an ancylostome. (Fig. 334.)

Life-history (Sandground).—The rhabditiform larva (0.3 mm.), with flagellar tail, hatches from the egg in soil, becomes sheathed, and the infective filariform larva (0.6–0.7 mm.) is formed. These can survive desiccation, reviving in water; thus they withstand drought. The larvae fail to penetrate human skin. Carbon tetrachloride and tetrachlorethylene are effective in treatment.

Superfamily: Trichostrongyloidea

Genus: *Trichostrongylus*

TRICHOSTRONGYLUS COLUBRIFORMIS (Giles, 1892) (Fig. 335)
and allied species

Distribution.—Normally, this is a parasite of the upper small intestine of the sheep and goat; it is not infrequently found in the duodenum and upper jejunum of man in agricultural districts of India, Central Africa, Egypt, Java,

Australia, Japan, Korea and especially in Abadan (Persia), where 70 per cent. of inhabitants are infested (Stewart). It has been found by Bonne in Java in scrapings from the duodenum, where the adults live with head embedded in the mucosa. By flotation technique the eggs of this species can be found in the fæces, together with ancylostomes (Lane), fairly frequently in India and Assam. Though rare in Europeans, the Editor once found them in a doctor and his wife from Kenya.

Characters.—The females (4–6.5 mm.) usually outnumber the males. They are very slender and pink, with an attenuated anterior extremity, and the vulva in the posterior quarter. The male (4–5 mm. by 0.07 mm.) has a bilobed

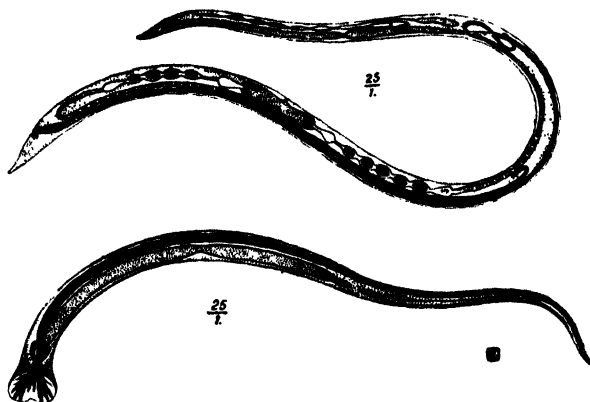


Fig. 335.—*Trichostrongylus colubriformis*. A, female ; B, male. $\times 25$.

copulatory bursa and two spicules. These parasites are found, a third to a half buried in mucus. When scraped on to a slide they appear as delicate red streaks. When the slide is shaken in saline in a Petri dish they can be seen against a dark background. The adult worms are never found in fæces. The mouth is unarmed.

The egg (63 μ by 41 μ) is relatively large, oval, thin-shelled, and contains a morula when deposited. (Plate XXVII, 15.) It is apt to be mistaken for that of *Ancylostoma duodenale*, but is translucent and smaller.

Life-history.—The eggs hatch outside the body; the rhabditiform larvæ metamorphose into infective filariform in six days at 22–25° C. and can be distinguished from similar stages in strongyloides and ancylostoma by the bead-like swelling at the tip of the tail. The semi-filariform third-stage larvæ are very resistant to desiccation. These enter the body *via* the skin or mouth, undergoing two ecdyses, and follow the same course as ancylostomes.

Pathogenesis and treatment.—Usually there are no symptoms, but the worms may cause secondary anæmia. They are expelled by tetrachlorethylene (*see* p. 796).

An Eastern form has been separated in Japan (*T. orientalis*). *T. probolurus* (Railliet, 1896) is rarely seen in man; it is a natural infection of the gazelle and camel.

Superfamily: Rhabdidoidea

Genus: *Strongyloides*

Fig. 336.—*Strongyloides stercoralis*. (After Faust.) Anterior end of parasitic male. b., buccal chamber; sp., buccal spines.

STRONGYLOIDES STERCORALIS (Bavay, 1876) (Fig. 336)

Distribution.—World-wide, especially in Brazil and Cochin-China. The parasitic form lives in the sub-mucous tissue of the small intestine.

Characters.—Until recently it was thought that embryos were produced by parasitic, parthenogenetic female, in the absence of a male, but it is now claimed that a parasitic male (Kreis, 1932) exists, shorter and broader than the female. The oesophagus is said at first to be filariform, but American observers claim that it is double-bulbed and this feature renders their claims doubtful. (Fig. 336.) Later, two copulatory spicules and a gubernaculum are said to become apparent and, when developed, the adult male resembles the free living form. (Fig. 337, 3.). Parasitic males

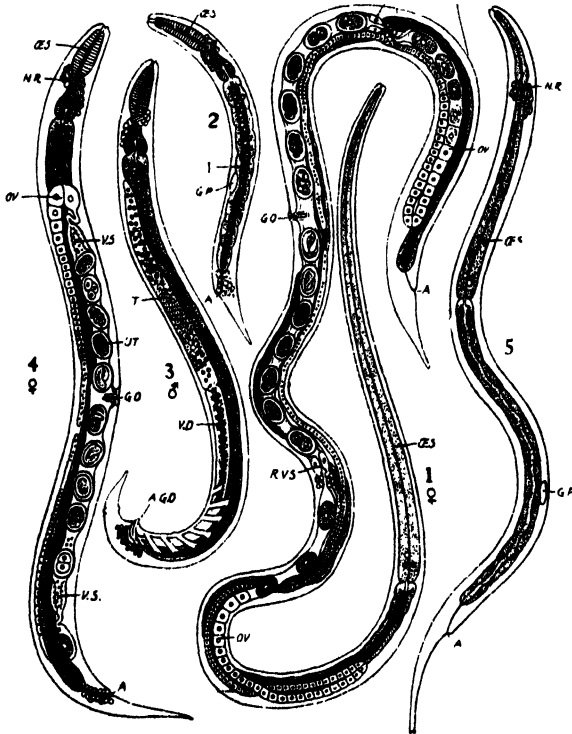


Fig. 337.—Life-history of *Strongyloides stercoralis*. $\times 30$. (After Looss.)

1, Parasitic female; 2, rhabditiform embryo; 3, fully-grown male; 4, fully-grown female; 5, fully-developed filariform larva.

A., anus; A.G.O., combined anus and genital pore; G.O., genital opening; G.P., primitive genital organs; I., intestine; N.R., nerve-ring; O., oesophagus; OV., ovary; R.V.S., rudimentary vesicula seminalis; T., testis; UT., uterus; V.D., vas deferens; V.S., vesicula seminalis.

are found in experimentally infected dogs, but not in human infections, due to the fact that they do not invade the intestinal wall and so are eliminated from the bowel soon after the females begin to oviposit. Although adolescent parasitic females may be inseminated, probably the majority are parthenogenetics. This is a process of *reversive metamorphosis*, in which it loses the ability of penetrating tissues and remains a lumen parasite.

Tanaka (1958) infected himself with 300 infective larvæ and had an eruption on the arm at the site of injection. Subsequently he had severe cough after 6 days, then various alimentary disorders until the 39th day. Eventually he cured himself with hetrazan.

The female (2.5 mm. by 0.034 mm.) (Fig. 337, 1) tapers anteriorly and ends in a conical tail. The mouth has three small lips and leads to an œsophagus occupying a quarter of the length of the body. The vulva lies in the posterior third. There is a prominent uterus containing 50 eggs ($50\text{--}58\ \mu$ by $30\text{--}34\ \mu$) which are laid in the lumen of the bowel in an advanced stage of development and may occasionally be found in the fæces. They hatch immediately to embryos (0.2–0.3 mm. by 0.013 mm.), which have a double-bulb œsophagus, apt to be confused with the rhabditiform stage of *Ancylostoma* and *Necator*. (Figs. 337, 2 and 338.) They are passed active in fæces, and in 3–5 days are converted into free-living male and female forms, both of which have a rhabditiform, double-bulb muscular œsophagus. The male is a free-living form (0.7 mm. by 0.035 mm.) (Fig. 337, 3), with the tail curved ventrally, two spicules and an accessory piece. The free-living form of the female measures 1 mm. by 0.05 mm. The vulva lies behind the middle of the body. The uterus contains thin-shelled eggs, measuring $70\ \mu$ by $40\ \mu$ (Fig. 337, 4). In a fatal case in a Senegalese child, Carmain and Deschiens found that one-third of the glands in duodenum had been invaded by strongyloides which consisted of females, embryos and eggs.

Copulation between the sexes takes place in fæces. The rhabditoid larvæ produced are indistinguishable from those derived from the parasitic female. After 3–4 days they develop into host-feeding, mature filariform larvæ, which are the infective stage, and re-enter the definitive host *via* the skin or buccal mucosa, as in *Ancylostoma* or *Necator*, but may remain alive in the soil for many weeks. The distinguishing feature is that the œsophagus in strongyloides larvæ is half the length of the body (Fig. 337, 5); in *Ancylostoma* and *Necator* it occupies about a quarter. Filariform larvæ find their way into the small intestine and develop into female parasitic form. Under unsuitable climatic conditions, the sexual phase in the fæces may be omitted, and rhabditiform embryos produced by the parasitic female may develop directly into filariform larvæ capable of infecting the definitive host. (Fig. 337, 5.). The larvæ of *S. stercoralis* may be confused with those of *Rhabditis hominis*, a free-living worm which may gain entry by accident to the digestive tract of man. These larvæ measure $240\text{--}360\ \mu$ in length by $12\ \mu$ in diameter and resemble the parent worm in shape and structure of the œsophagus. (Fig. 338, 4).

SUMMARY OF LIFE-HISTORY OF *S. stercoralis*

Female *parasitic intestinal* form gives rise to *eggs* which, hatching in intestinal canal, give rise to:—

First *rhabditiform larvæ* in fæces which, at high atmospheric temperature give rise either to:—

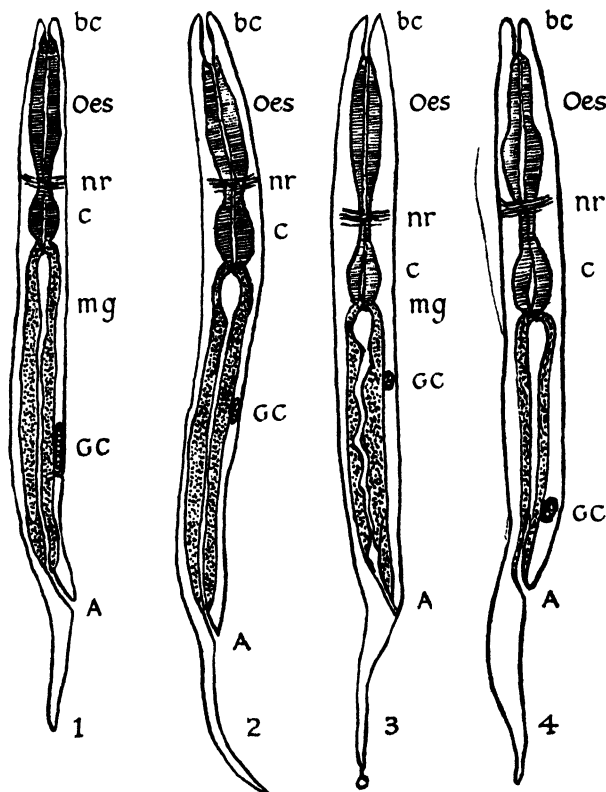
Infective or to *sexual* forms which copulate, and females lay *eggs* from which emerge

Second *rhabditiform larvæ* which moult and give rise to:—

Filariform larvæ which enter man by penetrating the skin or through the mouth, and migrate through the lungs to the œsophagus; on arrival in the pulmonary capillaries the larvæ produce hæmorrhages which form the avenue of

escape into the alveoli; followed by cellular infiltration into the respiratory passages with output of eosinophile cells. The changes result in strongyloides pneumonitis. These develop in two weeks into:—

Parasitic female and (possibly) male in the small intestine. The latter is said to be almost identical with the free-living form; the females differ by being slender, filiform, with a cylindrical oesophagus extending through the anterior third of the body.



1. *Strongyloides stercoralis*

2. *Ancylostoma duodenale*

3. *Trichostrongylus colubriformis*

4. *Rhabditis hominis*

A.=anus. b.c.=buccal cavity. Oes=oesophagus. C=cardiac oesophageal bulb. m.g.=midgut. G.C.=genital cells. nr.=nerve ring.

Characters	<i>Strongyloides</i>	<i>Ancylostoma</i>	<i>Trichostrongylus</i>	<i>Rhabditis</i>
Average size	225 × 16 μ	275 × 17 μ	275 × 16 μ	240 × 300 μ
Posterior tip	Blunt	Sharp	Sharp with head-like swelling	Sharp
Buccal chamber	Shorter, not longer than width at tip of head	Longer than width at tip of head	Longer than width at tip of head	as in <i>Trichostrongylus</i>
Genital primordia	Fairly large	Small	Very small	Very small

Fig. 338.—Distinguishing features of Nematode Larvae in the faeces.

Diagnosis is easy when the active larvæ in the faeces are recognized by their morphology. They are often found in diarrhoeic conditions, such as sprue. Duodenal intubation is the most certain means of diagnosis (Silva). When scanty the zinc sulphate flotation method of Faust may be used as it does not distort these larvæ.

Pathogenesis and treatment.—In large numbers this parasite produces irritation of the bowel and diarrhoea, probably also abdominal pain and flatulence. Desportes (1944), in self-infection, produced abdominal pains and lassitude after an interval of 26 days. Usually, it is found in men between 20 and 45 years old, in large numbers, coiled up in the intestinal follicles. Infected individuals show supersensitization to the antigens of this parasite (Fülleborn). Itchy urticarial wheals are produced by the entry of or by rubbing into the skin dried extracts of strongyloides larvæ. In the war in the Far East this worm infection was associated with periodic urticarial eruptions within one foot of the anus and often on the trunk and thighs. The eruptions were sometimes petechial, and sometimes linear like those of *Larva migrans*. They may be due to penetration of the skin by rhabditiform larvæ or some may be allergic (as above). In one case the larvæ have been found within a lesion, when abundant in the faeces. A suggestion has been made that as the lesions are so characteristic a particular strain of *Strongyloides* must be involved. Some observers have reported pulmonary complications with eosinophilosis, resembling tropical eosinophilia, but these require confirmation.

Miracil D (*Thioxanthone*, *Nilodin*) is said to give results. Gillet, de Smet and Nauman (1956) advocate 20 mgm. per kg. given in courses of 2–6 days, which they claim give 93 per cent. of cures. The most hopeful treatment is by Dithiazanine (see p. 88) as reported by Swartzwelder and others (1957). Success was obtained in 98·5 per cent. of cases. Out of 52 duodenal drainages on 18 patients no larvæ were found in 90 per cent. The dose is 200 mgm. enteric-coated tablets, three times daily for 21 days. There were no side effects. *Larva migrans* manifestations also clear up.

The prophylaxis is the same as that for *Ancylostoma*.

Strongyloides fülleborni, a parasite of the monkey, chimpanzee and African baboon and recovered by Wallace and colleagues from an American soldier in the S.W. Pacific, is identified by prominent vulvar lips and narrowing behind the vulva in the free-living females. The prominent oesophagus in the free-living stages is also characteristic.

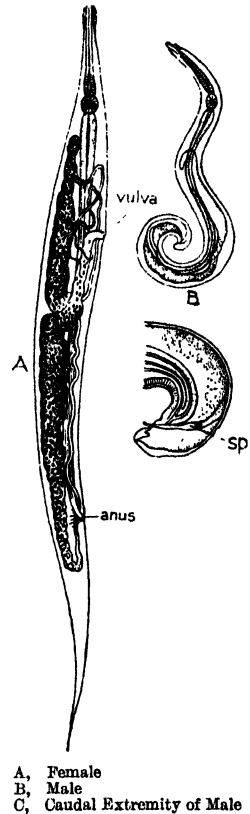
Superfamily: Oxyroidea
Genus: *Enterobius*

ENTEROBIUS VERMICULARIS (Linn., 1758) (Fig. 339)
“Threadworm or Pinworm”

Synonym.—*Oxyuris vermicularis*.

Distribution.—World-wide (45 per cent. of school children are infected). It lives in the upper part of the large intestine, especially the cæcum. Occasionally it is found in the female genital organs, rarely in the ear and nose. Chimpanzees, gibbons and marmosets can be infected (Sandosham).

Characters.—This is the only nematode of man with a double-bulb oesophagus in the adult. It is small and white, its mouth surrounded by a culticular expan-



A, Female
B, Male
C, Caudal Extremity of Male

Fig. 339.—*Enterobius vermicularis*. $\times 12$. (After Leuckart, in Brumpt's "Précis de Parasitologie.")

sion, and its skin transversely striated. The male is seldom seen, and does not migrate like the female. Much smaller than the female (2.5 mm.), its posterior third is curved spirally, and its caudal extremity blunt, with six sensory papillae and a single spicule, 70 μ (Fig. 339, c). The female (9–12 mm.) has a long pointed tail, the anus 2 mm. from the posterior extremity, and a transverse, slit-like vulva in the anterior fourth of the body. (Fig. 339, a.) The gravid female lays eggs in a stream of 10,000–15,000 in a few minutes and dies when egg-laying is completed.

The egg (50–54 μ by 20–27 μ) has a characteristic shape, flattened on one side, and is almost colourless, with a bean-shaped double-contour shell, which contains a more or less fully-formed embryo. (Plate XXVII, 19.)

Life-history.—There is no multiplication of worms inside the body. The egg shell is weakened by the intestinal juices and the larva breaks out of the shell. Soon afterwards it invades the glandular crypts and penetrates into the glands and stroma, where it coils up, causing some liquefaction of the tissues, but no cellular reaction.

According to Schüffner the length of life of *E. vermicularis* ranges from 37–93 days. As soon as the ovary becomes packed with eggs the female worm looses her hold on the intestinal wall and lies passive in the faecal stream. The fertilized female migrates out of the anus to deposit her eggs in the perianal skin and perinæum. The crawling of the gravid females produces intense pruritus. After few hours the embryo develops rapidly and attains a length of 140–150 μ . It is then ingested, generally as a result of deposits of faeces under the finger nails, conveyed to the mouth, and hatches in the digestive juices. Liberated larvæ after two months pass from the small into the large intestine, where they become mature. The whole cycle takes two weeks. Eggs can be inhaled through the nose from infected garments at some distance (Lentze), and embryonated eggs have been found in dust. Damp conditions with minimal ventilation are necessary for survival. Schüffner has described a process known as *retrofection*, in which infective larvæ re-enters the anus. The eggs require a six-hour exposure to air before they can hatch. In one-third of infected children the eggs are found in nail dirt. Adult worms have been found in a suppurating cyst in the female breast (Coovay).

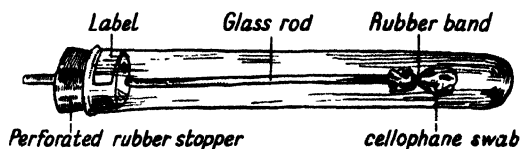


Fig. 340.—N.I.H. anal swab.

Diagnosis.—This is difficult unless the worms are seen; they may be found outside the anus at night. Occasionally eggs may be found in the faeces. The mature worms penetrate the mucosa and encyst in the submucosa of the large intestine or appendix, causing inflammation. They are thought to be the exciting cause of appendicitis in 2 per cent. of cases, and are then found in the lumen. There is no marked eosinophilia. Nasal itching is common, and pruritus ani is produced when the ova are deposited in enormous numbers near the anus. The worms may enter the vulva and cause a mucoid discharge, restlessness and insomnia. Familial infections are common. The number of parasites infecting a host is determined by the number of eggs swallowed. The adult worms are phototactic and are attracted by the light of the electric bulb during sigmoidoscopy. They may also be demonstrated in mucosal scrapes by proctoscopy.

A cellophane sprayer "N.I.H. swab" (Fig. 340) has been devised, by which it

is possible to obtain eggs by scraping the perineum (Hall). This device is much used in America. Enclosed in container, it is easily sent by post to be examined at leisure. The cellophane is mounted in water, or N/10 NaOH on a slide, and covered with a coverslip. The "Scotch Tape" method in which the eggs adhere to the sticky surface is very popular. A 2-2½ in. strip is held, sticky side out, with forceps, or placed over the butt end of a test tube. The perianal region is swabbed. A drop of toluene is placed on a glass slide and examined for eggs and adults.

Schöffner and Swellengrebel introduced the glass pestle method. A piece of thick-walled glass tubing about 1 cm. in diameter has a globe at one end, half of the surface of which is rough ground. The moistened globe is applied to the perianal skin with a rotary motion; the material is then dried on a slide and examined with cedarwood oil.

Treatment.—This is often difficult. Pruritus ani can be relieved by *Ung. hydrarg. ammon.* B.P. Quassia is also much used. After a salt-water enema, an infusion, 1 in 40 (10 ozs.), is injected slowly with the foot of the bed raised.

Piperazine hydrate, in the form of syrup, at dose of ½ gr. (11 mgm.) daily per year of life, is effective (White and Standen). The optimum dose level of 50-75 mgm./kg. daily. It is known as Piperazina, or Antepar Elixir (p. 877).

Piperazine adipate (Entacyl) is probably better for threadworm than the hydrate, in tablet form of 300 mgm.

The dose for children up to six is one tablet per day for every year of life.

For those over six and for adults the dose is two tablets after meals three times daily in a course extending over seven days. It may be necessary to repeat the course after an interval of one week. The maximum dose of entacyl is 3 grm. for an adult and 2 grm. for a child.

During the treatment the perianal area and the perineum should be smeared with ammoniated mercury ointment and the usual hygienic measures taken to avoid reinfection.

Dithiazanine (or Telmid; Eli Lilly), an American benzothiazole compound, has been found by Swartzwelder and colleagues (1957) to be the most efficient remedy. It is non-toxic and has no side effects and is given in enteric-coated tablets in doses of 200 mgm. thrice daily after meals for 5 days. The results were accurately checked by negative swabs (*see* p. 881).

Hexyl-resorcinol is popular in America, given by enema, 1 in 2,000 solution, after evacuation with a soap enema. Two pints are given to an adult, and up to the limit of tolerance in children. This is repeated every three weeks, and in two-thirds of the cases negative swabs are subsequently obtained. The drug gives no better results by mouth (*see* p. 797). (Wright, Brady and Bozicevitch.)

Prophylaxis.—General measures must be taken. It is advisable to make the child sleep in cotton drawers and cotton gloves, to pare the finger nails, and to wash the hands after defecation.

Superfamily: Trichinelloidea

Genus: *Trichuris*

TRICHURIS TRICHIURA (Linn., 1771)

Synonym.—*Trichocephalus dispar* "Whipworm" (Fig. 341).

Distribution.—World-wide, but more in the tropics than elsewhere. This worm is identical with a species found in pigs, and some monkeys (*Colobus rufofasciatus* and *C. diana*). In many countries it is present in more than half the population.

Characters.—The male (30–45 mm.) has an anterior attenuated portion, containing the cellular oesophagus, which is half as long again as the thicker posterior portion. The caudal extremity is curved ventrally through 360 degrees and there is a single spicule in the sheath, studded with spines. (Fig. 341, 3.)

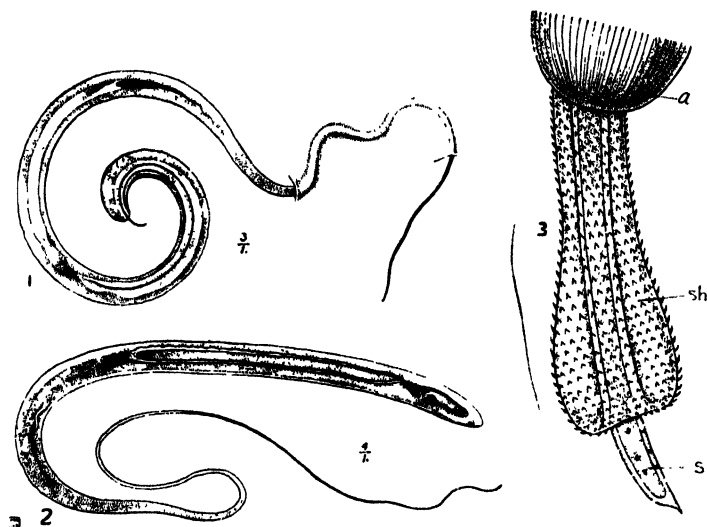


Fig. 341.—*Trichuris trichiura*. $\times 3$. (After Brumpt.)

1, Male, partly embedded in the mucous membrane of the intestine; 2, female; 3, copulatory apparatus, greatly magnified.

a, Posterior extremity of body; s., spicule; sh., sheath.

The female (30–50 mm.) has an anterior attenuated portion, twice as long as the posterior half, which is occupied by a stout uterus, tightly packed with eggs. A sacculate tubular ovary runs forward from the posterior end for over half the thick part of the body. Females preponderate over males in a proportion of 466 to 1.

The egg (50 μ by 22 μ ; Plate XXVII, 18) is brown and has a characteristic barrel shape, and a single shell with a plug at each end. It contains an unsegmented embryo.

The worm is greyish-white or slightly pink and lives in the cæcum, where it maintains its position by transfixing a superficial fold of mucous membrane with its slender neck, and lying embedded in mucus between the intestinal villi.

Life-history.—Infection is spread chiefly by stale feces. The eggs are unsegmented; embryonation takes at least 21 days, and the contained embryo develops very slowly, attaining its full size in 6–12 months depending upon the type of environment. It can withstand a low temperature owing to its thick shell, and remain latent for five years. Moisture is necessary and it cannot withstand desiccation. Development is direct. The embryo hatches only when the egg is swallowed: the egg-shell is digested by the intestinal juices, the larva emerges in the small intestine, penetrates the villi where it develops for a week, re-entering the lumen. It then passes to the cæcum or large intestine, where it attaches itself to the mucosa and becomes adult.

For treatment and pathogenesis, see p. 790.

Genus: *Capillaria*

CAPILLARIA HEPATICA (Bancroft, 1883)

Synonyms.—*Trichocephalus hepaticus*, *Hepaticola hepatica*.

This is closely allied to *T. trichiura*, and is normally a parasite of the liver of the rat, where the eggs are deposited in masses. They resemble those of the former, but the outer shell is distinctly pitted. It has a direct life cycle like that of *T. trichiura*. It has been found twice (Dive and MacArthur), the first in a British soldier in India. Septic pneumonia, secondary to abscess of the liver, was caused by the adult worms. The eggs are present in liver substance but not in faeces. Infection in rodents is due to cannibalism. The second was reported by Brosius in Panama (1948) in a woman who lived on the livers of rodents which harbour the parasite. This infection was cured by oil of chenopodium. Fain has recorded the parasite in the liver of 9 new hosts in Haut Ituri in the Belgian Congo. Eight of them were rodents and one a species of *Dendrohyrax*.¹

Genus: *Trichinella*

TRICHINELLA SPIRALIS (Owen, 1835). (Fig. 342)

Distribution.—World-wide, formerly common in Germany. Found in U.S.A. (in 5 per cent. of the pigs of Boston; with modern digestive technique, it has been found in 18·6 per cent. of cadavers in Michigan), China, India, Syria (from eating wild pig), in Algeria and East Africa. Recent recrudescence in England and South Wales was ascribed to sausages. Pigs, wild boars, bears (brown and polar), walrus and rats are universally infected. Most animals, even lizards, are capable of infection in the laboratory, but birds are refractory. Infection takes place from pig to rat, and rat to rat, as sick rats are eaten by their fellows. Man is not a normal intermediary host. Trichiniasis occurs more frequently in temperate than in tropical zones.

Characters.—*Trichinella* is a white worm just visible to the naked eye. The male (1·6 mm. by 0·04 mm.) has a cloaca situated posteriorly between two caudal appendages and two pairs of papillæ. The female (3·4 mm. by 0·06 mm.) has a vulva in the anterior fifth, an ovary in the posterior half, and an anterior portion occupied by a coiled uterine tube. The anus is terminal. She normally lives 30 days and produces 1,500 or more larvæ.

The egg (20 μ in diameter) lies in the upper uterus, but the embryo soon breaks loose from the shell and lives free in the uterine cavity. The embryos are voided into the lumen of the intestine and measure 100 μ by 6 μ .

The worm inhabits the small intestine. The embryos emitted by the female migrate into the muscles where they encyst. The cysts are too small to be seen at meat inspections unless they are completely calcified. The male dies soon after copulation, the female 5–6 weeks later after discharging hundreds of embryos.

Life-History.—When man consumes raw flesh infected with cysts of *T. spiralis* the cysts are digested out in the stomach and, after excysting in the duodenum, the larvæ invade the duodenal and jejunal mucosa and develop through four ecdyses into adult males and females within 5–7 days. Whilst both adults and larvæ develop within the same host, two hosts are required to complete the life cycle. In nature the infection is normally propagated by the black and brown rats, which are cannibalistic. Man usually acquires infection from eating inadequately cooked pork and also bear hams. In Polar regions the polar bear, arctic fox, walrus and bearded seals are affected. The embryos, derived from the female, travelling *via* the lymphatics and venous channels, guided by instinct, pierce the coats of vessels and encyst in striated muscles, especially the dia-

¹Morishita and Tani (1960), who have studied this parasite in monkeys, have found a case of *capillaria cutanea* in man. This is the first occasion on which this parasite has been found in the skin.

phragm, intercostal and laryngeal muscles and tendinous insertions in the neck and eye. The cysts are oval, the cyst wall being formed by tissue reaction (Fig. 343). At first the adult worms may be lodged in the glandular crypts, but later the females burrow into the villi, and even into the mesenteric lymph glands.

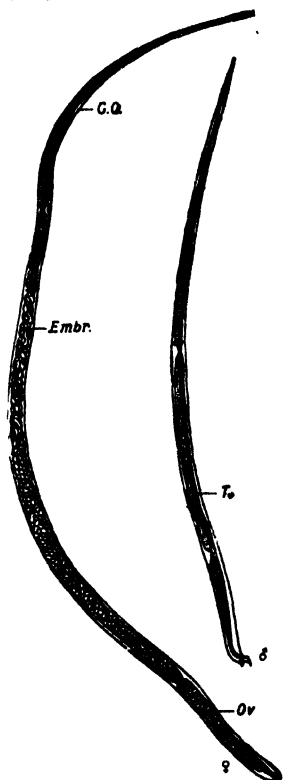


Fig. 342.—*Trichinella spiralis*, female and male. $\times 45$.
(After Brumpt.)
Embr., embryos; G.O., genital opening; Ov., ovary; T., testis.

Symptoms.—The symptomatology may be divided into three stages: (1) invasion (incubation), (2) migration of larvæ, and (3) encystation of larvæ and tissue repair. After an incubation period of 7–14 days the irritation of the duodenum and jejunum produces violent diarrhœa. There may be maculo-papular eruptions. In the second stage larvæ have been found in the cerebro-

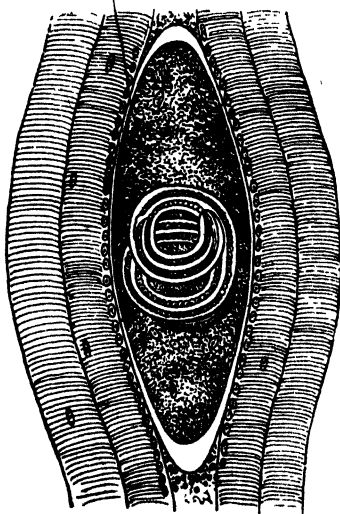


Fig. 343.—Encysted larva of *Trichinella spiralis*, fifteen days after entering muscle. $\times 300$. (After Claus, in Brumpt's "Précis de Parasitologie.")

spinal fluid and their presence is not always accompanied by clinical symptoms (Evers), but some patients exhibit signs of meningitis: others encephalitis. Symptoms at first may resemble those of cholera or dysentery with hyperpyrexia ($T. 104^{\circ}$ – 106° F.). During migration of larvæ through the tissues there may be typhoidal symptoms with remittent temperature, a slow muttering delirium, muscular rheumatic pains, and difficulty in mastication, deglutition and respiration. "Splinter" nail hæmorrhages are characteristic. Three weeks later, when encystment in muscles has taken place, there is profound cachexia, due to absorption of toxins, œdema of the face, abdomen and legs, mental apathy, pruritus and skin eruptions. Death occurs in the sixth or seventh week from exhaustion or pulmonary complications. In recovery, the fever resolves, but the muscular pains persist. In Wolverhampton cases (1940) there were no severe gastro-

intestinal symptoms, but abdominal pains, œdema of the eyelids and headache, suggesting influenza, and puffy face suggesting nephritis, with blood and albumin in the urine for a few days. Severe forms were described by Houston and Ross (1941) with hæmorrhages beneath the pleuræ and also in stomach and intestines, especially into the right psoas muscle. Myocarditis was one of the most serious complications. The mental attitude was identical with that of encephalitis. Splenomegaly was observed. Embryos were detected in the peripheral blood and could be demonstrated by mixing blood with dilute acetic acid and subsequent centrifugation. *In the period of encystation* there may be cachexia, toxic œdema or extreme dehydration. Nervous disorders include peripheral neuritis, defects of vision, delirium and encephalitis.

Diagnosis.—Eosinophilic leucocytosis appears soon after infection, and may be high; it decreases in the chronic stage, and is absent after nine years. Adult worms and embryos are found in the feces. In the chronic rheumatoid stage, cysts can be recognized under the microscope in biopsy material. When calcified they may be demonstrated by X-rays. At autopsy, the pectoral muscles, diaphragm and laryngeal muscles (Gould) should be searched. In America, 50 grm. of muscle is digested by artificial gastric juice at autopsy. In the living subject a small portion of tissue obtained by biopsy can also be digested, and this is the best method of demonstrating cysts. They are found in U.S.A. in 20 per cent. of the population; in England in 1 per cent. (Van Someren). "Subclinical trichiniasis" is now recognized as a definite entity.

The precipitin test (Bachman), made with extracts of the parasite, becomes positive too late to be of value. An intradermal reaction may be produced by antigen prepared from artificially-infected rabbit muscle. This when injected causes both immediate and delayed reactions. American workers use 1 in 10,000 dilution of antigen in Coca's solution, which is more sensitive and gives positive results two to three weeks after infection. The intradermal test (I.D.T.) has been given an eleven years' trial, and according to Kozar (1958), gives a positive reaction in 71.6 per cent. The antigen is made from *T. spiralis* larvæ from artificially-infected pigs.

Prophylaxis.—Rats in pigsties must be destroyed, and pork, especially sausages, inspected carefully. Bear meat has been prohibited in U.S.A. and in Russia. Areas with the highest proportion of garbage disposal to swine give the highest trichiniasis rates in man.

Treatment.—Injection of convalescent serum may control the toxic features. Good results have been observed after intravenous injection of 5 ml. of 10 per cent. calcium-gluconate (Lilly) during the migratory phase. A.C.T.H. diminishes symptoms and fever. Cobalt irradiations 10,000 γ cobalt-60 is a dose which does not prevent the larvæ from developing into adults, but does result in partial or complete sexual sterilization of the adult worms (Gould, 1955).

FILARIOIDEA

Superfamily: Filarioidea

This group includes spirurate filiform nematodes adapted to inhabit the deeper tissues, such as the circulatory, lymphatic and connective tissue layers. Some insect intermediary is necessary to complete their development.

Genus: *Wuchereria*

WUCHERERIA BANCROFTI (Cobbold, 1877, Seurat, 1921). (Fig. 344)

Synonym.—*Filaria bancrofti* (Cobbold, 1877)

Distribution.—This is wide in tropical and subtropical countries, reaching north to S. Spain, in Europe and Charleston in U.S.A., and south to the Argentine, Transvaal, Brisbane in Australia, with isolated foci in North Central Africa and Egypt; in East Africa along the coast of Tanganyika, in the region of the great lakes, especially at Mwanza—Lake Victoria, and south to the Transvaal. It is common in West Indies, Brazil, South China, South India, Ceylon, Indonesia and in Melanesia, Solomon Islands, and New Guinea.

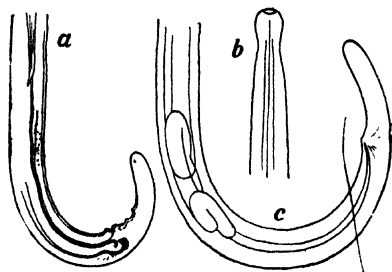


Fig. 344.—Parental forms of *W. bancrofti*. Magnified.

a, Tail of male; b, head and neck; c, tail of female.

Characters.—It is a thread-like white worm found in lymphatic vessels and glands. The sexes are coiled together, and can be separated with difficulty (Figs. 186, 187, p. 725). Buckley has shown that the cuticle is adorned with small cuticular bosses.

The male (4 cm. by 0.1 mm.) is coiled, with a corkscrew-like tail and two spicules, the larger of which measures 500 μ . The smaller (300 μ) is grooved on its ventral aspect. There is a short, thick proximal and a whip-like distal portion ending in a hook, and 15 pairs of minute sensory caudal papillae. A saddle-shaped thickening of the cuticle on the posterior wall of the cloaca forms a shield, and there is an accessory piece peculiar to *W. bancrofti* (Fig. 344, a). There are 12 pairs of circumanal papillae, of which eight are preanal and four postanal in position. There are also two pairs of large sessile papillae, and at the tail a solitary pair of minute size. The female (6.5–10 cm. by 0.2–0.28 mm.) has a tapering anterior end with a rounded swelling. There are sessile papillae on the head and an oral aperture leading to a cylindrical oesophagus. The mid-intestinal tube is one-third to one-fifth of the total diameter and opens into the rectum posteriorly. The caudal extremity is narrow and abruptly rounded (Fig. 344, c). The vulva is 0.8 mm. behind the anterior extremity. A swollen vagina (0.25 mm. in length) leads into the uterus, which divides into two tubuli, which are much coiled, occupying the greater portion of the body with a diameter three times that of the mid-intestine (Fig. 345). Two ovaries and ducts extend to within 1 mm. of the tail.

The eggs lie in the upper uterus enclosed in a chorionic membrane which becomes a sheath to the living embryos (microfilariae) (Fig. 346). They are emitted by the viviparous female and travel via the lymphatics into the blood-stream, whence they are abstracted by various species of mosquito. Their size in the distal part of the uterus is 38 by 25 μ , but as they are pushed to the vagina they become more elongated. The microfilaria develop from an oval egg and measure at first 216 μ . The embryo often lies curled up in its shell which becomes lobed, resembling a Dutch twist, or "Pretzel."

Embryo (microfilaria) $280\ \mu$ by $7\ \mu$.—Examined in the living state with a low power it appears structureless. With higher magnifications the entire embryo is seen to be enclosed in a sheath (structureless sac), which is longer than the enclosed embryo, so that this can move backwards and forwards, and the collapsed portion trails after the head or tail. The sheath has been the subject of controversy. It is generally held to be the outstretched vitelline membrane,

but in the microfilariae of *Litosomoides carinii* of the cotton rat it has been found that a true larval sheath is developed during its sojourn in the blood (Kershaw). In the middle third is some granular material, or primitive gut (*Innenkörper*). There is transverse striation of the muscular layer throughout. At one-seventh of the length from the head there is a break which denotes the nerve ring (n.r.) and one-fifth of the length there is a triangular V-shaped patch, demonstrated by light staining with dilute hæmatoxylin, known as "anterior V-spot," or the excretory pore and excretory cell (e.p. and e.c.). A short distance from the tail a second pore

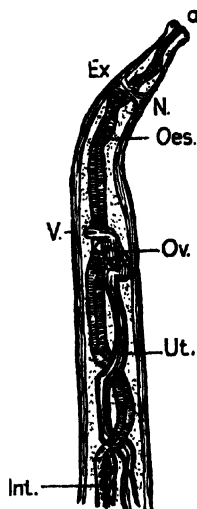


Fig. 345.—Diagram of head of *W. bancrofti* ♀. $\times 50$.

a., mouth; b., circumoral papillae; Ex., excretory pore; Int., intestine; N., nerve-ring; Oes., oesophagus; Ov., ovary; Ut., uterus; V., vulva.

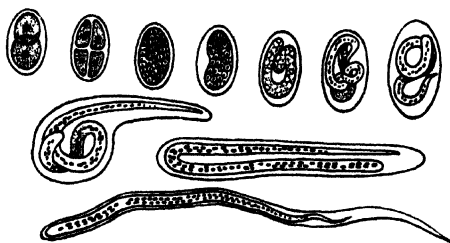


Fig. 346.—Evolution of sheathed microfilaria from ovum in uterus of parent worm. The later stages may occasionally take place after emission from vagina. (Partly after Penel.)

represents the anus, cloaca or terminal part of the primitive alimentary canal, and is known as the "posterior V-spot" (Fig. 351, 1). Deeply staining cells are known as genital cells (g.c.). When stained, the body of the embryo is seen to be composed of closely packed cells, and by focusing, when the movements of the living microfilaria have subsided, the head appears to be covered by a delicate prepucce. A short fang is from time to time shot out from the uncovered cephalic end and suddenly retracted (Fig. 190, p. 727).

Knott showed that microfilariae pass with difficulty through the peripheral capillaries and that they are less active in day than in night blood. They are capable of movement and of transit from place to place (Drinker).

Microfilaria vauceli. The microfilaria of *W. bancrofti* var *vauceli* is described by Gaillard from the West Coast of Madagascar. It differs in its smaller length $250\ \mu$, in the larger excretory pore and cells, in the disposition and size of the genital cells, which are larger, and in the larger anal pore. The "inner body" is granular. The attitude lacks the graceful curves of *W. bancrofti*. In certain respects it is intermediate between it and *malayi*, but differs in the absence of the two terminal nuclei in the tail and in the shorter cephalic space. It exhibits nocturnal periodicity.

Periodicity.—Microfilariae of *W. bancrofti* exhibit a nocturnal periodicity wherever they occur, in West Indies, South America, North, West and East Africa, China, Indonesia, New Guinea and Melanesia, i.e., they are present in peripheral blood in larger numbers during the night than during the day. The maximum concentration is from 10 p.m. to 2 a.m. It appeared to Manson that this nocturnal periodicity was an adaptation to the habits of night-biting mosquitoes—*Culex fatigans*, *C. pipiens* and certain Anophelines—but the mechanism has never been satisfactorily explained. The numbers of the

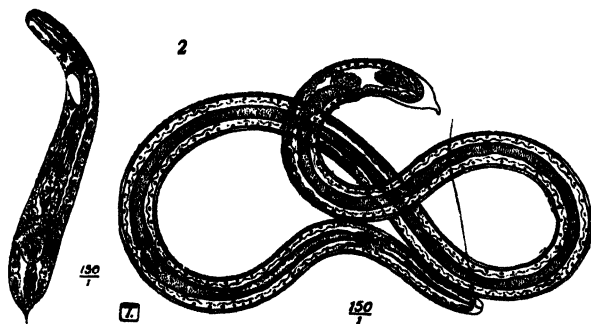


Fig. 347.—Stages of larval form of *W. bancrofti*, from thoracic muscles of *Culex fatigans*. $\times 150$. (After Looss.)

microfilariae are influenced by sleeping, and respond instantly to waking and bodily activity. By reversing the hours of sleeping and waking the periodicity is disturbed for three days and then reversed to diurnal periodicity (Mackenzie, 1886). Observations on microfilariae of animals (*Dirofilaria repens* of dog, filaria of American crow and that of the Malayan monkey, *Macaca speciosa*) show that they also maintain nocturnal periodicity and are sensitive to light and darkness, and reversal is easily established. Periodicity is probably a quality inherent in the microfilaria itself and persists unchanged in transfused blood. This was demonstrated by Knott (1935) in a patient injected with microfilaria-containing blood, and in whom they maintained a nocturnal periodicity for 14 days. Hawkings' results (1946) were less conclusive with nocturnal microfilariae, but Gönner in a self-transfusion experiment with 160 ml. of blood containing embryos of *L. loa* and *D. perstans*, found that the former persisted for 4 days and retained their diurnal periodicity, while the latter (non-periodic) remained in his blood for nearly three years.

Many years ago Manson had an opportunity of ascertaining that, during their diurnal absence from the peripheral circulation, the microfilariae retire principally to the larger arteries and to the lungs where, during the day-time, they may be found in enormous numbers.

Gaillard, in Indo-China, found that the surgical removal of 10 parturient female *W. bancrofti* made no appreciable difference to the microfilarial curve but that, on the other hand, severe physiological disturbances do. Various theories have been advanced by Fülleborn and others to account for this singular phenomenon, though none are entirely satisfactory. Yorke and Blacklock thought that obstruction to the passage of microfilariae through the cutaneous vessels is at a minimum at the end of the period of bodily activity and that the periodicity is therefore primarily dependant upon the variations in the actual supply of microfilariae to them. Considerable light has been shed upon

the mechanism and periodicity in general by the discovery by Hawking and Thurston of a non-sheathed microfilariæ in a monkey (*Macaca speciosa*). In the animal, as in man, the curve of microfilarial density in the venous blood follows closely that of the capillary blood. They have shown that an increase of microfilariæ in the blood at night is not a spurious effect, due merely to the congregation of the organisms in the capillaries of the skin, but to a true increase affecting all the circulatory blood, and it is due to the periodic liberation from accumulations in the small blood vessels of the lungs.

The nocturnal habit is retained by microfilariæ when blood is transfused into another filaria-free monkey (*M. speciosa*). Edeson and Wharton have shown that in the case of *B. malayi*, which is usually strictly nocturnal periodic, the microfilariæ of this species in the Kuantan district of Malaya do not show this feature so clearly and microfilariæ can be found in appreciable numbers in the day-time blood as well.

MacFadzean and Hawking (1956) proved clearly that the microfilariæ of *W. bancrofti* are affected by the oxygen concentration in inspired air and by muscular exercise, so that they disappear from the circulation. The effects of a general anæsthetic on the numbers of circulating microfilariæ has also been investigated by Hawking (1956). In *W. bancrofti* no influence was elicited, but it was otherwise in the diurnal circulating microfilariæ of *Loa loa* in whom a marked diminution was recorded, an observation which has since been confirmed by Duke. The response of *B. malayi* to oxygen content of blood is similar to that of the African *W. bancrofti* and a fall in the numbers occur, but no marked effect follows with increase of carbon dioxide in the inspired air. The non-periodic Pacific type in Fiji differs from that of periodic African *W. bancrofti* in that increased oxygen content of the blood brings about a slight rise of the microfilarial counts. (Edeson, Hawking and Symes, 1957). A curious agglutinative phenomenon has been described by Yoeli (1956) by the injection of anticoagulant (heparin) to the drawn blood. Intravenous injection of this substance during day-time releases microfilariæ of *W. bancrofti* into the peripheral blood for a short period. It is presumed that microfilariæ gather together in the capillaries and other vessels of the lung during their absence from the peripheral blood by the power of agglutination and thigmotaxis.

Life-history.—The life-history was first worked out by Manson in *Culex fatigans* in China in 1878. Within one hour of entering the mosquito's stomach, the microfilariæ cast the sheaths and bore through the stomach wall. O'Connor and Beatty showed that at the end of an infective feed the embryos collect at the anterior end of the stomach and then enter the anterior cylindrical portion of the midgut. Forward transportation is effected by reversed peristalsis until they are distributed over the whole of this cylinder. At the end of sixteen hours they form a writhing mass behind the valve which prevents their progress into the foregut. The proboscis of the mosquito exerts positive chemotaxis upon microfilariæ. Therefore *Culex fatigans* or *C. pipiens* can abstract more embryos than would be present in a similar quantity of circulating blood. The mosquito abstracts 1 c.mm. of blood at each feed and, in so doing, concentrates the embryos ten-fold. They next enter the thorax, where they lie between the muscular fibres (Fig. 349). Within two days they increase in girth, the "posterior V-spot" (or anal pore) enlarges, and the excretory vesicle

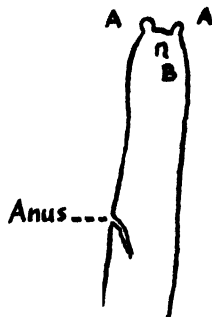


Fig. 348.—Larval filaria from proboscis sheath of *Aedes pseudoscutellaris*. A., terminal; B., postanal papillæ. Length 1.4 mm. \times 0.18 mm.

becomes more prominent. By rapid nuclear proliferation the larval filaria now assumes a squat "sausage" form (Fig. 347, 1), the tail shrinks and is then absorbed. Mouth and œsophagus are apparent from the fifth day onwards and the excretory pore is transformed into the anus. (Fig. 347, 2.). According to Iyengar the Gc.2 and Gc.3 cells (Fig. 351) divide several times and give rise to a column of cells which form the mid-intestine (large gut). The posterior intestine (rectum) is formed from four cells derived from the Gc.4 cell. The genital primordium is formed from the Gc.1 cell.

When the larva is 0.5 mm. in length, a bulbar œsophagus appears at the first and second fourths of the alimentary canal. Now, elongated and worm-like, the larva moves sluggishly about. Three caudal papillæ develop which function in progression and facilitate penetration of human skin (Fig. 348). About the tenth day (in favourable circumstances) the larval filaria, 1.4 mm. long, travels forward into the head, where it coils up and enters the proboscis sheath of the mosquito, but occasionally it may penetrate into the abdominal cavity and legs. Two or

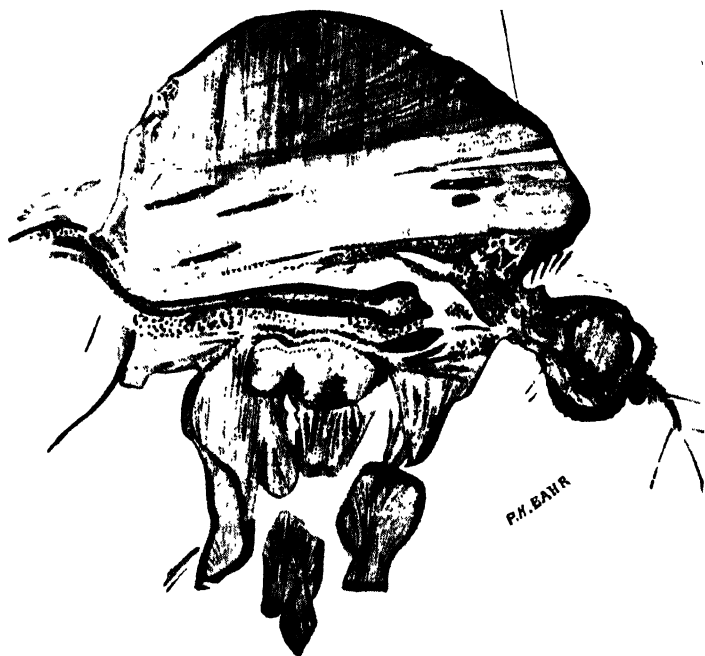


Fig. 349.—Section of thoracic muscles of *Aedes scutellaris* (*pseudoscutellaris*): second day after feeding on filariated patient.

more ecdyses take place. At high temperatures and in moisture the complete cycle occupies ten to fourteen days, but it is retarded to six weeks by cold. Sometimes the larvæ die in the thoracic muscles and are enclosed in chitin, producing a curious mummy-like structure (Fig. 194, p. 730). When an infected mosquito bites man, the larvæ, attracted by warmth, break through the terminal portion of the proboscis sheath at the *ligula*, as Iyengar has shown, at the central point of "Dutton's membrane," wriggle out on to the skin, which they penetrate near the seat of the puncture caused by the stylets of the mosquito (Fig. 350).

This was originally shown by the Editor in 1910 in a self-imposed experiment, but Iyengar (1956) carried out others to determine whether the mature larva can penetrate unbroken human skin. It was found that penetration was impossible and it is concluded that this occurs only from the labium of the mosquito. Complete development of *W. bancrofti* has been observed in the following species of mosquitoes:

- Culex fatigans* (*quinquefasciatus*). West Indies, British Guiana, India, Philippines, S. China, Egypt, Queensland, Celebes, Indonesia.
- C. pipiens* and *C. pipiens* var. *pallens*. China, Egypt.
- C. habilitator*. St. Croix, West Indies.
- C. alis*. Indonesia.
- C. whitmorei*. Indonesia.
- C. molestus*. Israel.
- C. vishnui*. Celebes, India.
- C. vagans*. China, N. India.



Fig. 350.—Larval *W. bancrofti*. Var. *pacifica* emerging from proboscis of *Aedes pseudoscutellaris*.

- C. annulirostris*. Indonesia.
- Mansonioides annulifera*. Southern India.
- M. longipalpis*. Malaya.
- M. africanus* and *M. uniformis*. Central Africa.
- Aedes togoi*. Japan.
- A. chemulpaensis*. Japan.
- A. poicilius*. Philippines.
- A. pembensis*. Is. of Pate, Kenya.
- A. aegypti* and *A. albopictus*. Indo-China.
- A. scapularis*. Brazil.
- A. vigilax*. New Caledonia and Australia.
- Anopheles subpictus*. India.
- A. nigerrimus*. Southern India and Ceylon.
- A. hyrcanus* var. *sinensis*. Japan, China, North-West India.

- A. funestus*. Nigeria.
- A. gambiæ*. West Africa.
- A. algeriensis*. Tunis.
- A. amictus*. Queensland, New Britain.
- A. albitarsis*. St. Croix, West Indies.
- A. albitarsis*. Brazil.
- A. aconitus*. Celebes.
- A. annularis*. India.
- A. barbirostris*. Dutch East Indies, Southern India and New Guinea.
- A. darlingi*. British Guiana.
- A. punctulatus farauti*. New Guinea, Solomon Islands, New Hebrides.
- A. squamosus*. Sierra Leone.
- A. stephensi*. India.
- A. sundaicus*. Sumatra.
- A. tessellatus*. Maldive Islands.
- A. vagus*. South India.
- A. varuna*. India.

Some 22 species are listed in which partial development may occur.

In the human host the infective larvæ pass through the peripheral blood vessels to the lymphatics where they become mature in an estimated period of three months to one year. Man is the only known definitive host.

In view of the fact that considerable confusion has been caused in recent years by the discovery of larval filariæ in wild-caught mosquitoes, in the course of surveys upon the natural infection rate, it has become necessary to differentiate between the larval characters of human and allied species of animal origin. It has to be realized that the filariæ of some animals, fruit bats and birds develop in those species of mosquitoes which normally transmit human filariasis.

Nelson, G. S. (1959) has shown that the infective larvæ of *W. malayi* is 1-2 mm. in length and has three poorly defined caudal papillæ; that of *W. patei* is about the same length and has a marked dorsal protuberance resembling a dog's head, in lateral position. The larva of *Dirofilaria corynodes* of monkeys, *Cercopithecus* and *Colobus*, from *Aedes pembraensis* has the typical cigar-shaped tail, but less pronounced narrowing between the anus and the extremity, with three small papillæ. The larva of *D. repens* of the dog and cat resembles the foregoing, but with only one terminal papilla: it develops in *Aedes ægypti*, *A. pembraensis* and *Mansonia africanus*; that of *D. immitis* of the dog from *A. ægypti* and *Culex fatigans*, cannot be distinguished from that of *D. repens*. The larva of *Setaria equina* of the horse, mule and donkey in *A. ægypti*, *A. pembraensis* and *Culex fatigans* is about the same length, but can easily be distinguished by one large terminal papilla and two subterminal ones, looking like little ears.

WUCHERERIA BANCROFTI VAR PACIFICA.—Manson-Bahr, 1941

The Editor first suggested that the filaria found in Central and Southern Pacific might be a separate species. As far as can be ascertained, embryos (microfilariae) are morphologically identical with those of *W. bancrofti*. Certain small differences have been noted in the morphology by Buckley (1952). The average length is smaller—females 58 mm, males 27 mm. The tail of the female lacks the bulbous swelling which characterize those from British Guiana. The anterior end of the Fijian specimens is oval in outline.

Microfilariae in Polynesians (Fiji, Samoa, Tonga, Cook Islands, New Caledonia) are non-periodic. In these islands as well as in Tokelau, Wallis, Ellice, Gilberts, Marquesas and those beyond "Buxton's line" (longitude 170° E.) they do not exhibit nocturnal periodicity, but occur in equal numbers in the blood by day and

night. Development of this filaria is confined to mosquitoes indigenous to the S. Pacific Islands, *Aedes scutellaris pseudoscutellaris* and *A. s. polynesiensis* (Marks), in both of which maximum development occurs. Recently a third

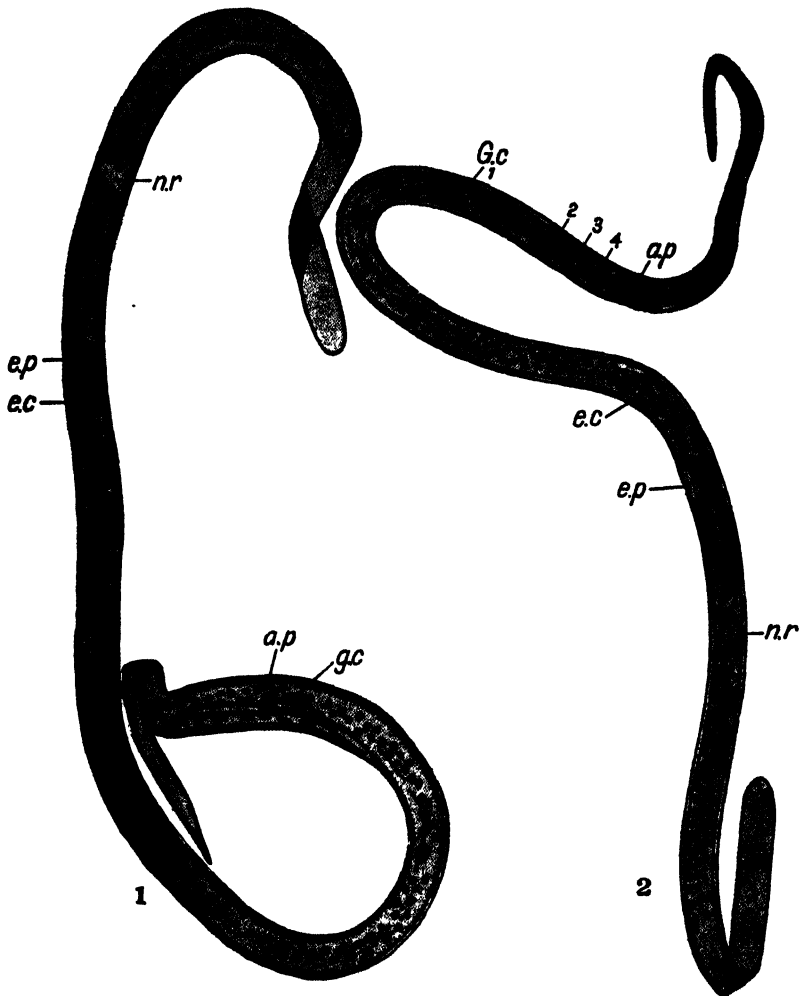


Fig. 351.—(1) *Microfilaria bancrofti*; (2) *Microfilaria malayi*. (From "A Comparative Study of Anatomy of *Microfilaria Malayi* and *Bancrofti*." Feng.)

nr. = nerve ring; *ep.* = excretory pore; *ec.* = excretory cell; *gc.* 1. 2. 3. 4. = "genital cells"; *a.p.* = anal pore.

species, *A. fijiensis*, has been incriminated by Symes. The non-periodic microfilaria does not develop readily in *C. fatigans*, which is the optimum host for the nocturnal periodic form, *W. bancrofti*. *A. s. pseudoscutellaris* and *A. s. polynesiensis* are adapted to the coconut palm and have peculiar habitats (see p. 1061). In immigrants to Fiji nocturnal periodic microfilariae

(Solomon Islanders, New Hebrideans, Ocean Islanders and Indians) retain their nocturnal periodicity, but, if members of these races are infected locally in Fiji, the microfilariæ found are non-periodic. In Europeans, Indians and in others contracting filariasis in Fiji the microfilariæ also are non-periodic. This form of filaria produces enlargement of lymphatic glands, especially the epitrochlear. The adult filariæ are for the most part found in lymphatic glands. Chyluria and lymphuria are rare. In New Caledonia the vector of this form is *Aedes vigilax*, a species which is also found in N. Australia and Queensland. The peculiarity of this local filariasis is that, though the microfilariæ rate is high (34 per cent.), filarial disease as seen elsewhere is practically unknown.

Genus: *Brugia*, Buckley, 1959

BRUGIA MALAYI (Brug, 1927) Rao and Maplestone, 1940

Distribution.—This is the common form in Malaya, Indonesia, Central India Ceylon, South China, Korea, Indo-China and Koshima Island, Japan. (It has not been found in Africa, America, Australia or in the Pacific Islands.)

Characters.—Rao and Maplestone described the adults (1940) in Travancore; later (1941) Bonne and colleagues in Indonesia. They are practically identical with *W. bancrofti* in nearly all characters; the females are indistinguishable. The female measures 55 mm. in length by 160 μ . The vulva is situated 0.92 mm. from the anterior extremity. The caudal end is bluntly rounded. The male is 22–23 mm. in length by 88 μ in diameter. The posterior extremity has about three turns and the anus is 0.1 to 0.14 mm. from the tip of the tail. One pair of large papillæ are just in front of the cloaca and one behind. There are also two smaller pairs. There is a small naviculate gubernaculum and two spicules which are unlike in size and structure. The longer is 0.34 to 0.36 mm.; the shorter 0.11 to 0.12 mm. in length. There are morphological differences in the microfilariæ and the mosquito intermediary is distinct—*Mansonioides annulifera*. Poynton proved that it is identical with the microfilaria of the "kra" monkey (*Macaca irus*) which is transmitted by the same mosquitoes. It is common in domestic dogs and cats in Malaya (Buckley) and has been found also in the Slow Loris (*Nycticebus coucang*), the banded leaf monkey (*Presbytes melalophos*) as well as in the Pangolin (*Manis javanica*).

The microfilaria of *B. malayi* was first discovered by Lichtenstein in Celebes, and was studied further by Brug in 1927. Brug and de Rook found the natural infection of the mosquitoes, *Mansonia longipalpis* and *M. annulatus*.

The animal representative of *B. malayi* is widespread. It has been found in cats in the island of Pate in N. Kenya by Buckley, but not in humans who are infected with *W. bancrofti*. Although the human form of *B. malayi* is common in dogs and cats in Malaya, yet there is a species, *B. pahangi*, which is confined to these animals and which has distinctive morphological characters (Fig. 352).

It has been shown by Edeson and Wharton (1957) that the human form of *malayi* can be transmitted to cats by the bite of *Mansonia longipalpis*. The period of full development of the adult filaria in this animal varies from 81 to 96 days before microfilariæ appear in the blood. The adult forms recovered from the cat correspond to the descriptions of *B. malayi* in man. *Malayi*-like microfilariæ have been found in cats in—Orissa, India (Raghavan, 1956), while dogs and the genet cat are infected in Pate Island, Kenya, suggesting that the animal reservoirs vastly outstrip human infections. According to Wilson (1958) the nocturnal periodic form in Malaya does not develop well in cats and is transmitted by species of Anopheles and Mansonia. The semi-periodic form occurs in man and commonly in cats, in freshwater swamps and forest. It is transmitted by *Mansonia annulatus* and *uniformis*. He thinks that, on the whole, the periodic microfilaria is longer than the semi-periodic.

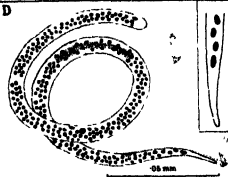
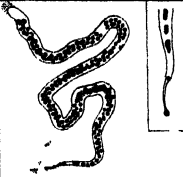

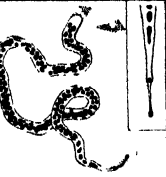
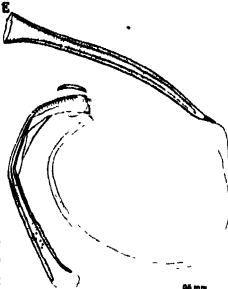

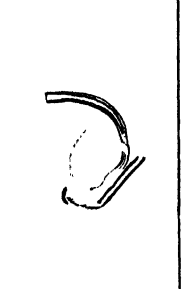

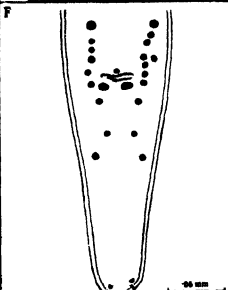
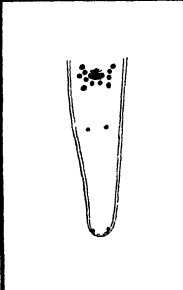
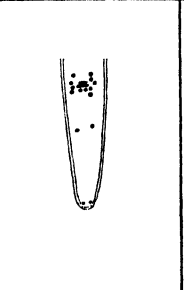
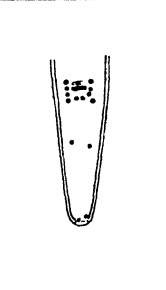
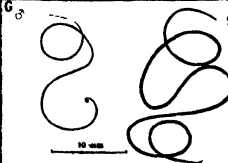
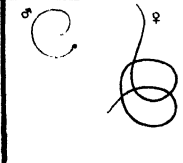
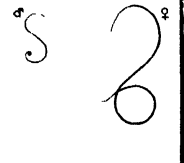
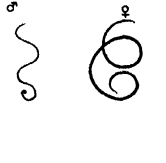
WUCHERERIA SILVA ARALJO, 1877		BRUGIA BUCKLEY 1960		
<i>W. BANCROFTI</i> (CONSOLID, 1877)		<i>B. MALAYI</i> (SILVA, 1937)	<i>B. PAHANGI</i> (BUCKLEY & EDSON, 1954)	<i>B. PATEI</i> (BUCKLEY, NELSON & HENICH, 1962)
A MAN		MAN, CAT, MONKEYS, *LORIS *MUSANG	CAT, DOG, TIGER, LORIS, MUSANG, WILD CAT,	DOG, CAT, GENET- CAT.
B CULEX Spp. AEDES Spp. ANOPHELES Spp.		MANSONIOIDES Spp. ANOPHELES Spp.	MANSONIOIDES Spp. ANOPHELES Spp.	AEDES Spp. MANSONIOIDES Spp.
C EQUATORIAL BELT		INDONESIA, MALAYA, INDIA, CEYLON, CHINA	MALAYA	AFRICA
D 				
E 				
F 				
G 				

Fig. 352.—Diagram, after J. C. Buckley, showing the morphological distinctions between the genus *Wuchereria* and *Brugia*.

(By permission of Ann. Trop. Med. and Parasit.

- A. Definitive hosts
- B. Intermediate hosts
- C. Geographical distribution
- D. Microfilariae and (inset) tail nuclei of microfilariae
- E. Spicules of males, lateral view
- F. Tails of males, ventral view
- G. Adult worms, actual size

* Experimentally infected only.

In view of these recent discoveries, Buckley (1959) has created the new genus *Brugia* which now contains three representatives—*B. malayi*; *B. pahangi* and *B. patei* (see Fig. 352).

Microfilaria malayi has a nocturnal periodicity like that of *W. bancrofti* (Brug, Poynton, Hodgkin, Gaillard, Liu, Feng and Yao). It is nocturnal on the West Coast of Malaya, but non-periodic in the Kuantan district (Edeson and Hawking, 1957) on the East Coast. It measures 200–250 μ by 5–6 μ . Its chief points of distinction are the elongated nucleus at the tip of the tail and the absence of nuclei in the cephalic space. (Fig. 351, 2.)*

The following table summarizes the main points of distinction between *microfilaria malayi* and *microfilaria bancrofti*:

TABLE XIII

MICROFILARIA MALAYI (Fig. 351, 2)	MICROFILARIA BANCROFTI (Fig. 351, 1)
It is often found closely folded with head close to tail, and is irregularly disposed for, besides major curves, minor angulations are typical.	Usually seen lying with head and tail well separated, and commonly shows three or four major curves of graceful appearance.
The nuclei are blurred and intermingled so that they cannot be easily counted.	The nuclei are well defined and spaced and can be easily counted.
The tail tapers to a fine point, continued as a fine thread. There is typically one nucleus at the extremity of the tapered portion and two in the terminal thread.	The tail tapers to a point and the terminal portion contains no nuclei.
The cephalic space is twice as long as broad.	The cephalic space is as long as it is broad.
The excretory pore and cell are separated.	The excretory pore and cell are close together and a thread of protoplasm runs posteriorly from the latter.
The anal pore is a clear space about 40 μ from the tail end.	

Treatment.—In *B. malayi* hetrazan clears the microfilariae in the blood in the same doses as for *W. bancrofti*.

Life-history.—The most favoured mosquito intermediaries belong to the genus *Mansonioides* (p. 1058) which are crepuscular or nocturnal feeders. Development in the mosquito is similar to that of *W. bancrofti*, but more rapid, in 6–8½ days. Difficulties have been encountered in Malaya in distinguishing larval forms of ornithofilariae of birds from those of human *W. malayi* in the routine dissection of mosquitoes. No development takes place in *Culex fatigans* (Gaillard). In China and Korea the appropriate species is *A. hyrcanus* var. *sinensis*; in Malaya, *Mansonioides annulatus*, *M. annulifera*, *M. longipalpis* and *M. uniformis* are equally suitable, being adapted to water plants, to the roots of which the larva adhere by their respiratory siphon. (Fig. 412, p. 1059). In Koshima Island, Japan, development takes place in *Aedes togoi* (Sasa and Hayashi, 1953).

The larval form of *B. malayi* in *Mansonia* undergo two ecdyses. The buccal cavity is formed from the cephalic space: the cesophagus from the nuclei of the anterior part of the nuclear column, the rectum and anus from the four G cells of Rodenwaldt and the anal pore. The premature genital pore mass is derived from the nuclei of the "Innerkorper." The muscles of the body wall from the so-called "subcuticular cells" of Rodenwaldt. The tail of the microfilaria, with

* Microfilariae *malayi* have also been found in the tiger, the flat-headed cat (*Felis planiceps*), Malay Civet cat (*Viverra zibethica*). *B. pahangi* has been transmitted to man and produced microfilariae capable of developing in mosquitoes and transmissible to a cat. (Edeson, Wilson and Wharton, 1960).

its two nuclei, is shed with the first moult. As in the case of *W. bancrofti*, the larva, when in the thoracic muscles, feeds by absorbing food through the cuticle. It does not feed at the expense of these muscles as has been stated. (Fig. 353).

Relationship to *W. bancrofti*: the two species exist together, especially in South India and Malaya. The incidence of the latter is urban: that of *B. malayi* rural, depending on the presence of ponds with decaying matter and water plants. In towns *W. bancrofti* has a centripetal and *W. malayi* a centrifugal distribution. In South India Iyengar finds that, under natural conditions, *W. bancrofti* develops in *Culex fatigans* and *Mansonioides annulifera*. In Malaya, on the other hand, the species are *Anopheles vagus* and *A. barbirostris*. In S. Korea and in the Island of Quelpart, Senoo and Lincicome found it in 12 per cent.

Pathology.—Filariasis due to *B. malayi* produces especially elephantiasis of the legs (p. 745).

Prophylaxis.—Eradication of water plants necessary for the development of mansonioides has proved effective.

Genus: *Dirofilaria*

DIROFILARIA MAGALHÆSI (R. BLAND, 1895)

This filaria was discovered in Rio de Janeiro in 1887 in the left ventricle of the heart of a child. For a long time its classification and significance remained obscure. Then Faust and his colleagues (1941) reported a similar discovery in a negress in New Orleans. The specimen was a solitary male closely allied to, if not identical with, the dog heart worm, *Dirofilaria immitis* and is transmitted by *Culex fatigans*, *C. annulirostris* *Aedes ægypti* and *Aedes polynesiensis* in the Pacific. This filaria may therefore sometimes occur as an accidental infection in man. The female is 155 mm.; the male 83 mm. in length.



Fig. 353. — Development stage of *Wuchereria malayi*, showing terminal nucleus in tail. (After Feng, 1936.)

Genus: *Mansonella*

MANSONELLA OZZARDI (Manson, 1897: Faust, 1930)

Synonym.—*Filaria ozzardi*; *F. demarquayi*.

Distribution.—West Indies, South America, Northern Provinces of Argentina (20–30 per cent. infected). Common in St. Vincent (West Indies) in aboriginal Indians (Caribs) of British Guiana, often together with *Dipetalonema perstans*. It was originally discovered by Manson in the blood of Carib Indians, and is now considered identical with *F. demarquayi*. The parental forms were discovered by Daniels in Demerara Indians and by Galgey in St. Lucia.

Characters.—The male, 3.2 cm., has a coiled tail and one spicule. The female (6.5–8.1 cm. by 0.21–0.25 mm.) has a vulva 0.76 mm. from the anterior extremity, and an anus 0.23 mm. from the tail. The caudal extremity has two prominent papillæ with a terminal thickened cuticle. The worms live in body cavities, embedded in adipose tissues. The microfilaria (173–240 μ by 4–5 μ) is unsheathed and closely resembles that of *D. perstans*, but has a sharp tail. (Fig. 185, 6, p. 724.) Mazzotti, by transfusing 100 ml. of blood containing 120,000 microfilaria, has determined that they can live in the blood of the recipient for more than 2 years (1957).

Life-history.—This was worked out by Buckley (1934) in St. Vincent, British West Indies (37·7 per cent. of the inhabitants infected). The intermediary insect is a midge, *Culicoides furens* (see p. 1063), a common pest; 27·5

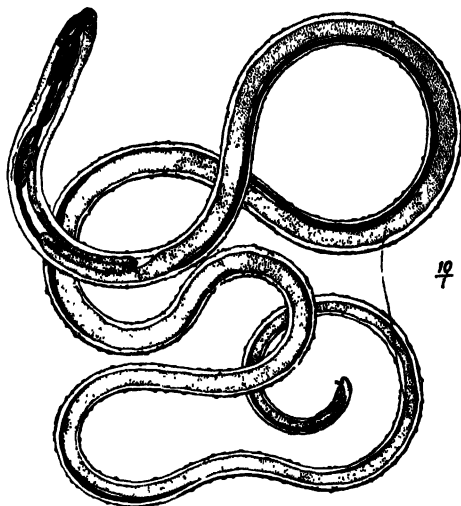


Fig. 354.—*L. loa*, male. $\times 10$. (Partly after Looss.)

per cent. experimentally infected contained larval forms of this filaria. The ingested microfilariae migrate within twenty-four hours to the thorax; developmental stages are similar to those of *T. perstans*. Two ecdyses occur; the largest—third stage—larvæ in the head measure 0·7 mm. Emergence from proboscis takes place within eight days. *C. parvensis* is possibly a vector in St. Vincent; *C. furens* in Antigua (O'Connor).

Pathology.—Montestruc (1949) thinks that it causes adeno-lymphocele.

Treatment.—Microfilaria ozzardi is susceptible to hetrazan; 6 mgm. per kg. but reports are so far conflicting. Hawking thinks that it is not effective.

Genus: *Loa*

LOA LOA (Guyot, 1778) (Figs. 354, 355 and 207, p. 755.) "The eye-worm"

Distribution.—Widely distributed in West Africa from Sierra Leone southwards to Angola; mostly along courses of great rivers, Niger, Wellé, Congo (not in East Africa); especially common in Southern Nigeria and on Ogowé River, Cameroons. In Southern Sudan a closely allied form, *L. papionis*, is found in baboons (*Papio cynocephalus*). In the Cameroons one-third of one hundred and fifty monkeys investigated harboured a filarial infection indistinguishable from *L. loa* (Gordon).

Characters.—The body is filiform, cylindrical, whitish and semi-transparent, with numerous round, smooth, translucent protuberances of the cuticle, 12–16 μ in diameter, and 9–11 μ above the surface. These chitinous bosses are more numerous in females. Their distribution is irregular. In the male they are absent at the extremities; in the female they extend on the tail and also the cephalic end. The mouth is unarmed and destitute of papillæ; there is no distinct neck, but a shoulder 0·15 mm. from the mouth where there are two

papillæ, one dorsal, the other ventral. The alimentary canal commences at a funnel-shaped mouth as a slender straight œsophagus, going on to an intestine $65\ \mu$ wide, and a short attenuated rectum. The male (3–3.4 cm. \times 0.35–.43 mm.) has its maximum breadth anteriorly (Fig. 354); posteriorly it tapers to a tail.

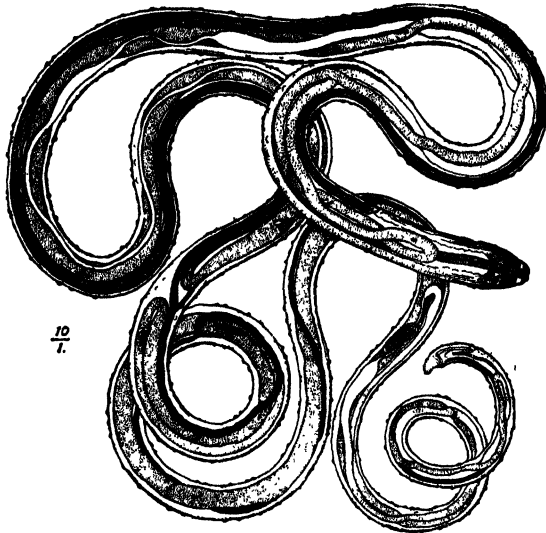


Fig. 355.—*L. loa*, female. \times 10. (Partly after Looss.)

which is curved ventrally, with two lateral expansions of the cuticle (0.7 mm. \times 0.029 mm.) (Fig. 356) In the middle, 0.03 mm. from the tail-tip is the opening, of the ano-genital orifice with two unequal spicules (123–176 μ and 88–113 μ) surrounded by thick labia. There are four large globular, pedunculated papillæ, decreasing in size antero-posteriorly, and a fifth pair of small postanal papillæ.

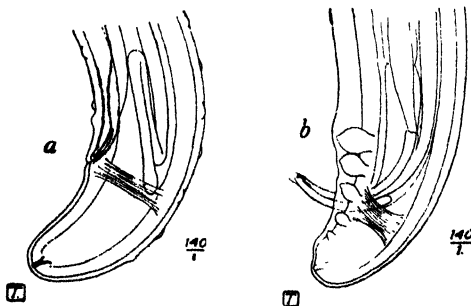


Fig. 356.—Posterior extremity of *L. loa*, (A) female, (B) male. (After Looss.)

The female (5–7 cm. \times 0.5 mm.) has a straight, attenuated, broadly rounded posterior extremity and a vulva 2.5 mm. from the anterior extremity placed on a small eminence. The vagina, 9 mm. long, branches off into two long uterine tubes extending through the length of the body. At the narrow end are the ovaries, with eggs in all stages. (Figs. 355 and 356A.) Reproduction is ovoviviparous;

the embryos develop within the egg envelope and uncoil themselves on expulsion from the vagina. When dead the adult worm often becomes cretified.

The embryo is known as *microfilaria loa*, or diurna, and is similar in size ($298 \mu \times 7.5 \mu$) and structure to *microfilaria bancrofti*. In fresh blood it may be impossible to distinguish them. In dried stained films (1) it assumes a stiff angular attitude, (2) the tail end is disposed in a series of sharp flexures, giving it a corkscrew appearance, with the extreme tip flexed, (3) the nuclei of the central column of cells of *microfilaria loa* is larger and less deeply stained. (4) The cephalic end of the column is more abruptly terminated. (Fig. 185, 2.)

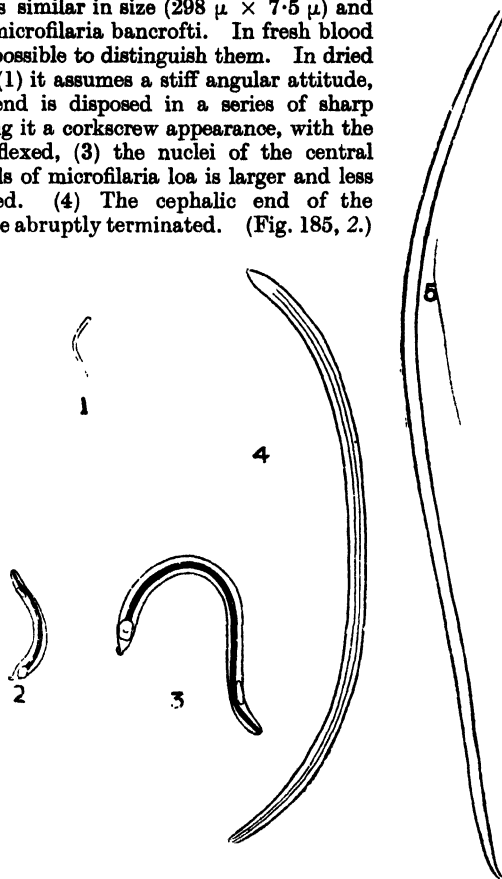


Fig. 357.—Development of *Loa loa* in chrysops. $\times 30$.

1, Larva, 24 hours old; 2, fourth day (length 390μ); 3, fifth day; 4, seventh day (length 1.5 mm.); 5, tenth day (length 2 mm., breadth 0.025 mm.).

(After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med.")

By special staining methods a large genital cell at the beginning of the posterior third constitutes a marked feature. *Microfilaria loa* takes up methylene blue (1 in 5000) in ten minutes. (Sharp, 1923.) In *microfilaria bancrofti*, absorption is much slower, but it shows up the excretory pore. *Microfilaria loa* may not be found in the peripheral blood until six or even seven years have elapsed from the primary infection. It is strictly diurnal (Chart 29, p. 756), from 8 a.m. to 8 p.m.—the reverse of *microfilaria bancrofti*. Inversion of periodicity takes place very gradually, as, for instance, when daily observations are made on a voyage round the world (Külz).

Life-history. (Fig. 357).—This proceeds in much the same manner as in *W. bancrofti*, but in the thoracic muscles, connective tissue and fat-body (Stevenson) of the bloodsucking "mangrove flies," *Chrysops silacea*, *C. dimidiata*, *C. langi*, *C. longicornis* and to some extent in *C. centurionis*. (Fig. 423, p. 1066) in W. Africa (Cameroons) and in the S. Sudan *C. distinctipennis*. On entering the stomach the embryo casts its sheath in three hours, and, piercing the stomach wall, enters the thoracic muscles and fat-body of the thorax, but principally that of the abdomen. Development is complete in ten days. In three days it becomes broad and torpedo-shaped; on the 4th and 5th days the squat-form is lengthened to 0.8–1 mm.; on the 6th, the corkscrew-like appearance is replaced by gentle curves. Then occurs the first ecdysis, and the sharp tail is replaced by a rounded trilobed extremity. By the 10th day it measures 2 mm. \times 0.025 mm. and 3 ecdyses have occurred. Larvæ congregate in the head in large numbers, the majority at the root of the proboscis, and make their way on to the skin of the human host by piercing the proboscis sheath when the fly feeds (Fig. 358). It is capable of carrying infection for five days. In Calabar 3.5 per cent. of wild-caught chrysops are found naturally infected with *Loa loa*. When an infected fly feeds, large numbers of infective larvæ emerge and are deposited on the surface of the skin, from which they disappear rapidly, by burrowing in. Escape of the larva is usually made by stripping the membrane joining the hypopharynx at the base of the labium. In the mammalian host the worms migrate along the inter-fascial planes. Lavoipierre has shown that the worms, on the way to the head, proceed along the hæmocele spaces and avoid air sacs. Infective forms rarely penetrate the brain.



Fig. 358.—Development of *L. loa* in *Chrysops silacea*, showing several mature larvæ at tip of labella.

(After A. and S. L. M. Connal, "Trans. Roy. Soc. Trop. Med. and Hyg.")

Development of the adult form in man was formerly thought to occupy 6–18 months, but the period is about 3 months (Duke) in experimental monkeys. Fully adult worms may be found in almost all anatomical regions, but which are limited by connective tissue. In monkeys similar worms have been demonstrated moving along intermuscular septa and similar fascial planes. Many patients with loiasis appear to have no microfilariae in the blood, but in reality they are present in small inconstant numbers and can be detected by repeated examinations. Gordon suggests that microfilariae may accumulate as a reservoir in the internal organs.

The systematic situation in regard to *L. loa* is much the same as in *B. malayi*. The reservoir hosts of *L. loa*, in the high rain forest of the Cameroons, are the forest monkeys. The filaria develops in *C. langi* which lives in the forest canopy, rarely attacking man, but plays the chief part in transmitting the parasite to monkeys. Wild monkeys, free from *L. loa* at the time of capture, develop loiasis when inoculated subcutaneously with infective forms of *L. loa* obtained from

dissection of naturally-infected chrysops. It appears probable that they all belong to the same species. There may exist physiological differences which may prevent interchange of the parasites amongst the human and monkey populations (Gordon, 1955). Chrysops, the intermediary, ingests from 10–20 ml. of blood per meal and feeds to repletion once every 14 days (the gestation period is 12 days). It is a "pool feeder," straining the blood from the subcutaneous hemorrhages caused by its bite.

Pathogenesis and treatment (see pp. 756–759).

Genus: *Tetrapetalonema* (Faust, 1935)

TETRAPETALONEMA PERSTANS

(Manson, 1891; Railliet, Henry and Langeron, 1912) (Fig. 359).

Synonyms.—*Filaria perstans*: *Acanthocheilonema perstans*: *Dipetalonema perstans*.

Distribution.—It is generally distributed throughout Central Africa in man and chimpanzee. Christy (1903) suggested the association of this parasite with banana plantations. In Congo, Nigeria, Gold and Ivory Coasts, Sierra Leone, Northern Rhodesia, Uganda (90 per cent. infected); also in Venezuela, Trinidad, British and Dutch Guiana (but not in West Indies), Amazon Valley (Brazil) and Northern Argentina; possibly also in New Guinea. It is found in Europeans in Central Africa, commonly associated with microfilaria loa and bancrofti; and in British Guiana with microfilaria ozzardi. As individual measurements differ so considerably, the South American form may well constitute a distinct species (Map XI, p. 723). This microfilaria was described by Manson in 1891 and the adult form subsequently by Daniels in British Guiana. It is found in the chimpanzee and gorilla. Allied species occur in New World monkeys. The adult worms live in body cavities in the peritoneal, the pleural and in the pericardial sac.

Characters.—It has a long cylindrical, smooth body, and a simple, unarmed mouth. The tail in both sexes is characteristic: incurvated, with a chitinous covering at the extreme tip split into two minute appendages, giving a mitred appearance. (Fig. 359.) Chabaud has pointed out that the female possesses four cuticular appendages at the posterior extremity, not two as hitherto believed.

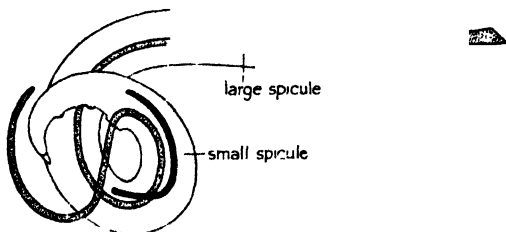


Fig. 359.—Tail of *Tetrapetalonema perstans*, showing two unequal spicules and papillæ. (After Leiper.)

The male (4.5 cm. by 0.06 mm.) is smaller than the female. The head is 0.04 mm. in diameter, and the cloaca has four pairs of pre-anal and one pair of postanal papillæ, and two unequal spicules (Fig. 359). The female (7–8 cm. by 0.12 mm.) has a cub-shaped head 0.07 mm. in diameter, and a vulva situated 1.2 mm. from the head. The anus opens at the apex of a papilla in the concavity of the curve formed by the tail; its diameter is 0.02 mm.

The microfilaria ($200\ \mu$ by $4.5\ \mu$) is unsheathed (Fig. 185, 5, p. 724). It possesses in a remarkable degree the power of elongation and contraction. Therefore the measurements vary considerably. Brumpt *et al.* described long and short forms (90 – $110\ \mu$ by $4\ \mu$). It is smaller than microfilaria bancrofti or loa and its caudal end is truncated and abruptly rounded. The tapering tail extends two-thirds of the entire length. The anterior "V-spot" is $30\ \mu$ from the anterior extremity. There is no marked tail spot, no central granular mass, and no cephalic prepuce. It moves freely in the blood, locomoting like the sheathless forms of microfilaria bancrofti. The microfilariae are found mostly in the heart, lungs, aorta and large vessels and spleen; rarely in the pancreas.

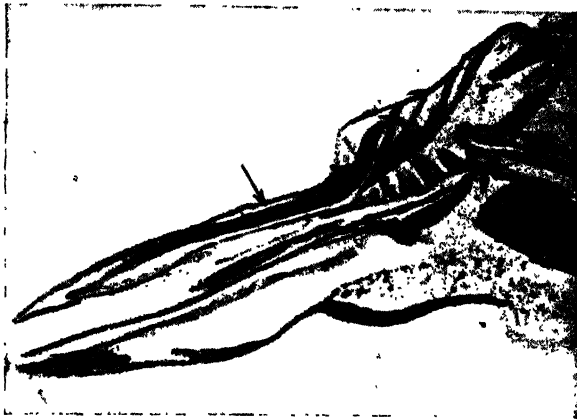


Fig. 360.—Larva of *Tetrapetalonema perstans* in proboscis of *Culicoides austeni*. (Dyce Sharp.)

The embryos occur in equal numbers both by day and night, according to the self-inflicted experiment of Gönner this embryo can persist in the recipient three years after blood transfusion.

Life-history.—Dyce Sharp described development in midges, *Culicoides austeni* (Fig. 360) and also to a lesser degree in *C. grahami* (Hopkins and Nicholas). It proceeds in the thoracic muscles, and, within six to nine days, the larval filariae ($0.7\ \text{mm.}$) are ripe for emergence from the proboscis. Before they emerge they cause a globular expansion of the labrum of *Culicoides* which then collapses and gives exit to larval filariae; 7 per cent. of wild-caught midges are infected in the Cameroons. Although Henrard and Peel have thrown doubts on this, the validity of Dyce Sharp's work has now been confirmed in the Cameroons by Hopkins and Nicholas (1952).

Pathogenesis.—Adult worms occur singly in the mesentery, perirenal and retroperitoneal tissues and pericardium. This filaria may cause transient pains in the gall-bladder region. It is occasionally found in subcutaneous cysts. The Editor has made some observations which indicate that an allergic reaction, which resembles "Calabar swellings," may sometimes ensue. The incubation period is nine months to one year.

Treatment.—There have been conflicting reports on the action of hetrazan on *T. perstans*, but McGregor and colleagues, in the Gambia, found it was killed by 5 mgm. per kg.

Genus: *Dipetalonema*

DIPETALONEMA STREPTOCERCA (Macfie, 1922)

Synonym.—*Agamofilaria streptocerca* (Macfie and Corson, 1922: Stiles and Hassall, 1926). *Acanthocheilonema streptocerca*.

Macfie described this sheathless microfilaria, found commonly in the corium of the skin, but not in the blood, of Gold Coast natives (22 out of 50 in Accra).



Fig. 361.—*Dipetalonema streptocerca* embryo, showing characteristic curvature of tail. $\times 200$. (Dyce Sharp.)

It probably has a wide distribution, especially in the Cameroons. The microfilaria (Fig. 361) is distinguished by the "walking-stick handle" of the tail extremity (Dyce Sharp). It is 215μ in length. The arrangement of nuclei in the head and the four prominent ones in the tail constitute an index of differentiation from the microfilaria of *O. volvulus* and *T. perstans*. Development takes place in *Culicoides grahami* and is similar to that described for *D. perstans* (Henrard and Peel, 1949).

Peel and Chardome found microfilariae in the skin of 6 out of 11 chimpanzees (*Pan paniscus* and *P. satyrus*) in the Belgian Congo. Two adult female worms found in the connective tissue were closely similar to *T. perstans*. The microfilariae of this species, *T. vanhoofi*, closely resemble those of the latter. The incubation period of *D. streptocerca* is 3-4 months. Wanson and others (1951) have shown that the microfilariae are very susceptible to hetrazan and disappear from the skin in less than 48 hours. Duke (1957) in British Cameroons, has described an acute vesicular eruption on arms and shoulders of a European in which microfilariae of *D. streptocerca* were demonstrated. The infection proved susceptible to hetrazan.

TETRAPETALONEMA BERGHEI n. sp. (Chardome and Peel, 1951)

This is found in Belgian Congo together with *D. streptocerca*. It is a white nematode $60.9 \text{ mm.} \times 0.271 \text{ mm.}$ with almost imperceptible striations. Head is hemispherical and a relatively large genital opening is situated anteriorly. The uterus divides into two branches. Microfilariae in all stages are visible in the uterus. There are several enlargements of the body at intervals. The caudal extremity narrows rapidly showing four excrescences. The tail is recurved. The microfilaria which is found in the skin resembles that of a small microfilaria *perstans* and measures $179 \mu \times 3.55 \mu$. It may be that the adult form may turn out to be similar to *T. perstans*.

Genus: *Onchocerca*

ONCHOCERCA VOLVULUS (Leuckart, 1893: Railliet and Henry, 1910) (Fig. 362)

Distribution.—West Africa, Sierra Leone to Angola, Congo, Katanga, North Kenya, Southern Sudan, Tanganyika, Mexico, Guatemala, Central America, N.E. Venezuela (Sucre and Monagas, 250-1,000 metres).

Characters.—The body is white and filiform, tapering at both ends. The head is rounded. The cuticle is marked by transverse ridges, and raised, with prominent angular and oblique thickenings, more distinct posteriorly. It is

usually found in nodules, but can reproduce outside them (Van den Berghe). The male (2-4 cm. by 0.2 mm.) has a straight alimentary canal ending in a sub-terminal anus. The tail ends in a slight spiral, and is bulbous at the tip. There are two pairs of pre-anal, two post-anal, an intermediate large papilla, and two unequal spicules (82 μ , 77 μ) protruding from the cloaca (Fig. 362); the former has a fluted end and the latter a narrow neck and knob. The female normally measures 60-70 cm. by 0.4 mm., but is often smaller, 35-40 cm. (Schäfer). The head is round and truncated (0.04 mm.), the vulva 0.85 mm. from the anterior extremity, and the tail curved. Cuticular striations are not so marked as in the male. It is ovoviviparous and the egg has a striated shell with a pointed process at each pole (like an orange wrapped in tissue paper) measuring 30-50 μ in diameter. Usually males outnumber females by 2 to 1 (four males and two females in each tumour). (Brumpt separated a South American form as *O. cæcutiens*, which is said to differ in the size and shape of the papillæ in the male and in the size of the spicules; but this is doubtful.)

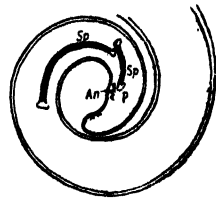


Fig. 362.—Caudal extremity of *Onchocerca volvulus*, δ . (After Brumpt.)

Sp., Spicules; An., Anus;
p., Papillæ.

The *microfilaria* (300 μ by 8 μ) are sheathless and are found in the fluid of the cyst-cavity and in the surrounding skin: they are of two types, large and small (Blacklock). The body tapers from the last fifth and ends in a sharply-pointed, recurved tail (Fig. 185, 4, p. 724). In the anterior fifth is a marked anterior V-spot. The cephalic cone is thickened at the commencement of the nuclear column. This microfilaria is non-periodic; it is found in skin, in the femoral, inguinal and cervical lymph-glands and in the expressed juice of tumours, but rarely in blood (2 per cent.). It is also present in the skin of widely-separated portions of the body in apparently healthy natives, without producing any nodules or tumours. Microfilaria are easily demonstrated in the skin by biopsy. They are often associated with eye symptoms, in the absence of tumours, and, by aid of the slit lamp, may be seen in the cornea, sometimes in association with massive elephantiasis of the legs.

Life-history.—This was worked out by Blacklock, in Sierra Leone, where 45 per cent. of the inhabitants are infected. Development takes place in the "buffalo gnat," *Simulium damnosum* (Fig. 419, p. 1063) and in *S. neavei* in Kenya. The fly abstracts microfilaria from the deeper layers of the skin near the nodule; they then enter the stomach, pierce its walls, and pass to the thoracic muscles where they undergo further development. During growth one or more ecdyses take place. At the seventh day the larva measures 0.65 mm. Development has been traced to the tenth day when the larva escapes from the proboscis; *Simulium* is a day-biting gnat (6 a.m.-6 p.m.) and 2.6 per cent. are naturally infected. They probably attract and then abstract microfilaria by scraping the skin with their prestomal teeth.

In the South American form development is similar to that of the Central African, but occurs in *Simulium metallicum* (*avidum*), *S. ochraceum* and *S. callidum* (*mooseri*), which are common in endemic areas in Guatemala. Developing larvæ are frequently found in the abdomen and Malpighian tubules of these flies. Two caudal papillæ are seen in fully developed larvæ, which measure 0.45-1.14 mm. In Guatemala 11 per cent. of *simulium* are naturally infected.

For pathogenesis and eye symptoms (keratitis punctata and interstitial keratitis) see p. 767.

Superfamily: Dracunculoidea.

Genus: *Dracunculus*.*DRACUNCULUS MEDINENSIS* (Linn., 1758). "The Guinea-Worm"

Distribution.—This is a common parasite of man in India, Arabia, south-eastern regions of U.S.S.R., Korea, Sudan, Africa, especially Gold Coast; it has been imported into West Indies and South America, and is now endemic in Brazil and Guianas. Occurrence in the ox, horse, dog, wild-cat, jackal and leopard in Rhodesia is probably accidental. Dogs, monkeys and cats can be experimentally infected. In one endemic area—Bahia, Brazil—the parasite has died out as the result of extreme drought which dried up all the wells.



Fig. 363.—*Dracunculus medinensis*. ♀ One-third nat. size.

Characters.—The female is the thickness of a knitting needle and usually 2 feet in length (32.5 cm. \times 1.5–1.7 mm.; 90 cm. is probably exceptional, but 120 cm. has been recorded by Ewart). It lives in connective tissues, and does not harm its host until about to produce its young, when it exhibits "geotropism," i.e., it is drawn towards earth, towards the limbs—to the fingers, if in the arms; to the scrotum or penis, if in the abdomen; to the breasts in the female, though 90 per cent. migrate to the legs and feet, especially behind the outer malleolus.

The body is cylindrical, white and smooth (Fig. 363). The tip of the tail is pointed, forming a blunt hook which was formerly thought to be used for holding firm in tissues, but this is not correct. The head is rounded, terminating in a thickened cuticle cap or "cephalic shield." The mouth is triangular, small and surrounded by six papillae and an outer circle of four double papillae. A lateral pair of cervical papillae is situated behind the nerve ring (Fig. 364). There is a single-bulb oesophagus. The secretion from the head glands is very irritating.

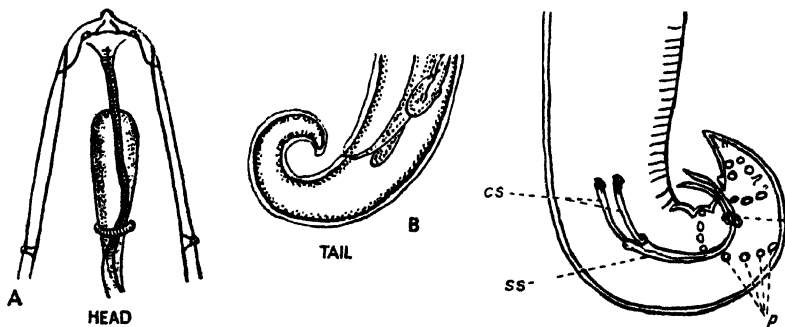


Fig. 364.—A, Anterior end and B, tail of *D. medinensis*. ♀ and, C, posterior end of ♂. \times 10. (After Faust.)

Ventro-lateral aspect, showing unus *u*, copulatory spicules *cs*, distribution of pre-anal and post-anal papillae *p*, and spicular sheath *ss*.

and blisters the skin of the host. The alimentary canal is small and is thrust to one side by the branched uterus. There is no definite anus. The vulva is difficult to see and has been only recently discovered as a very small tube in the centre of the worm. The whole worm is occupied by the double uterus packed with embryos (Fig. 365). The coiled uteri, distended by 3 million larvæ, fill the body. There is a double ovary and double oviducts at the posterior extremity. When doused with water, waves of contraction force the uterine contents forward, and then the thickened cuticle gives way and the "cap" is blown off. The uterus is extruded up to a length of $\frac{1}{2}$ inch; this also bursts and the contained embryos are shed into the water. The worm dies when its nervous system is destroyed. The sinus containing the dead worm easily becomes septic, but it may coil itself round tendons and, if pulled upon, breaks. It often becomes cretified and can then be demonstrated by X-rays.

The male is known from a single specimen in man 40 mm. in length, but was discovered by Moorthy (1937) in experimental dogs. It measures 1.2-2.9 cm. by 0.4 mm., has sub-equal spicules (490-730 μ), and a gubernaculum (200 μ).



Fig. 365.—Transverse section of *D. medinensis*, showing contained embryo.
(After Leuckart.)

The posterior end is coiled on itself one or more times. There are ten pairs of caudal papillæ of which four are preanal and six postanal. The copulatory spicules are subequal, 490-730 μ in length. After copulation it dies and is absorbed. It lives in between the muscles of the groin. Copulation probably takes place in the deeper tissues.

The embryo (Fig. 366) measures 500-750 μ by 17 μ and shows transverse striations of the cuticle. It is flattened, not cylindrical, with a long, slender tail, and a rounded head. The alimentary canal has a rudimentary anus and a bulbous œsophagus. There are two glands at the root of the tail. In water the embryos cannot swim, but sink and coil up and release again, moving by side-to-side lashing of the tail and tadpole-like movement of the body. Abnormal embryos, with prominences on the dorsal and ventral caudal surfaces, are not uncommon (Moorthy), but do not survive long.

Life-history.—In water they live for six days; in muddy water or moist earth two to three weeks. If slowly desiccated, they can be revived by water. They are swallowed by *Cyclops* when coiled up in rounded masses (*cyclops* has

a very small mouth). The efficient intermediaries are *Cyclops quadricornis*, or allied species (*C. strenuus*, *C. viridis*, *C. coronatus*, *C. bicuspidatus*, *Mesocyclops leuckarti* and *M. hyalinus*), but in the true tropics *Tropocyclops multicolor* and other species; in S. Nigeria it is *Thermocyclops nigerianus*. Jerky movements

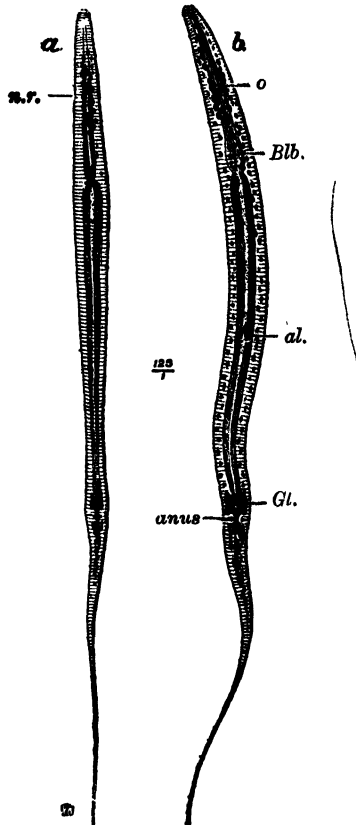


Fig. 366.—Embryo of *D. medinensis* $\times 150$.

a, Side view; b (after Loose), front view: oes., oesophagus; Blb., bulb; al., alimentary canal; Gl., glands; n.r., nerve ring.

of the embryo attract cyclops as a trout is attracted by a fly. As many as twenty may be found in one crustacean, but usually they die out when there are more than four. The pointed tail penetrates the gut wall; they then migrate into the body cavity and feed on the ovary or testes of the cyclops. There is no growth in size, but two to three ecdyses take place. The tail is absorbed and they become cylindrical and the posterior extremity trilobed. Development takes four to six weeks, but the larva may survive for four months. When 1 mm. in length they acquire a simple muscular oesophagus (Fig. 367) and the tail is truncated. This distinguishes the infective stage.

Cyclops is swallowed by man; in the gastric juice the body of the cyclops is dissolved and the larvæ become active and burst out. Onabarimo (1956) has to some extent cleared up the migration of the early stages in the mammalian host. It takes 3-4 months for the full development of both sexes. Immature stages were recovered 43-48 days whilst undergoing the fourth ecdysis. The route of the larvæ from the alimentary canal to the subcutaneous tissues of the mammalian host takes place via the lymphatic system. The worms reach the subcutaneous tissues by the 43rd day. In this situation the sexes live in equal numbers and sexual differentiation is distinct, though the males have not developed spicules. The final ecdysis takes place in the subcutaneous tissues. The adult worm takes one year to develop. In some Indian villages 38.6 per cent. of the cyclops are infected (Liston); in Dahomey an even higher percentage has been reported (Chatton). The average life of a cyclops is about 3 months, but those infected do not usually survive for more than 2.

The guinea-worm is limited to certain parts of the tropics by its need for suitable species of cyclops, and by the nature of the water supply. There is a regular rhythm of infection during one or two months of the year—January and February on the Gold Coast—during and at the end of the dry season. An infected cyclops is not active, but lies prostrate at the bottom of wells. Therefore in the dry season the buckets bring up many more infected cyclops and the liability of natives to infection is increased. Infection is easily controlled. Any filtration of water, even through a handkerchief, will remove the crustaceans. The native practice of bathing guinea-worm ulcers at the side of wells should be prohibited. Wells should be provided with a parapet and they should be sealed, and pumps erected.

Fedchenko (1869) is credited with the discovery of the transmission of the guinea-worm, but probably Manson was the original observer (1895). Leiper believes that the stages figured by the former are those of *Cucullanus*, not of *D. medinensis*.

For pathogenesis and treatment, see pp. 772-778.

Superfamily: Thelazioidea.

Genus: *Thelazia*.

THELAZIA CALLIPÆDA (Railliet and Henry, 1910)

Synonym.—*T. conjunctivæ* (Bose, 1919)

This parasite occurs commonly in the conjunctival sac of dogs in India and has also been found in horses, cats, oxen and camels. There are some 10 records in man, since it was discovered by Rhodes (1818) in the eye of an ox in France. Most of the records are from China, India, Korea and California. Most have been in the conjunctiva. The most complete account is by Martin Friedmann in *Ophthalmologica* (1949). Adult worms are ivory white, 4.5-13 mm. \times 0.25-0.75 mm. for males, and 6-17 mm. \times 0.8-0.83 mm. for females. The cuticula is plaited with transverse striations with sharp edges. The head end is adorned with papillæ. The life-history is unknown; that development may take place in the cockroach and land snails have also been suggested.



Fig. 367.—Larvæ of *D. medinensis* in body-cavity of cyclops.
(After R. P. Strong.)

III. Medical Entomology

PHYLUM ARTHROPODA

Order: Acarina (Ticks and Mites).

Class: Arachnida.

Genus: *Sarcoptes*.

Sarcoptes scabiei (Linn. 1758). Itch-Mite (Fig. 368)

Morphologically similar species are found on domestic animals, foxes, wolves, and llama.

Scabies.—Scabies is widespread in the tropics, especially in North Africa.

The female (0.3–0.4 mm.) of *S. scabiei* is bigger than the male (0.2 mm.). The sexes may be further distinguished by the epimer of the second pair of hind-legs which unite near the sexual orifice in the male; in the female they are free. There are suckers (ambulacra) on the much reduced legs of the female, and on the first, second and fourth legs of the male. The gravid female lays eggs in a burrow in the skin. The greater part of the surface of the female is covered with fine transverse folds. The upper surface bears a number of specialized

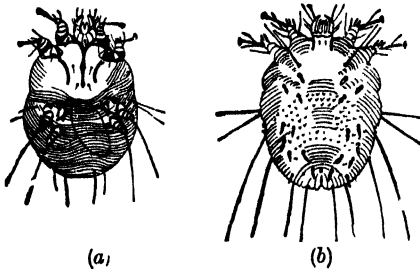


Fig. 368.—*Sarcoptes scabiei*: (a) ventral aspect with egg. $\times 35$. (After Canestrini.) (b) dorsal view. $\times 40$. (After Brumpt.)

spines and conical scales.

The oval eggs measure $150\ \mu$ by $100\ \mu$; in three to five days they give rise to larvæ and nymphs which live like adults, and pass through four stages in three weeks. Finally the nymphs moult, become sexually mature, and pair off on the surface of the skin. The average life of the adult is four to five weeks.

Sarcoptic mange (Animal scabies).—This is sometimes contracted by contact with dogs, cats and cattle infested with their own biological races of sarcoptes. They may be distinguished from human scabies by the distribution of papules and vesicles on the arms, shoulders, trunks and thighs, and by the absence of burrows on the hands. Sarcoptic mange is much more amenable than scabies to treatment with sulphur compounds.

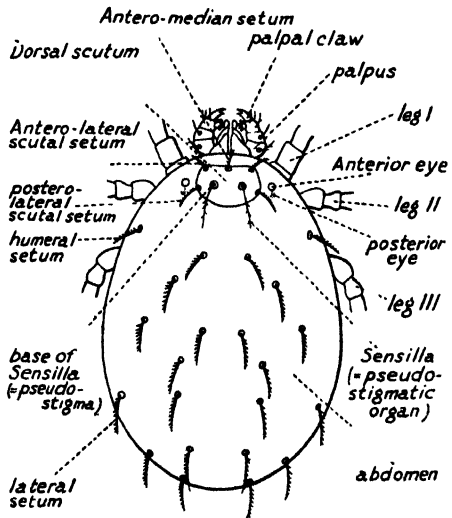


Fig. 369.—Anatomical features of a Trombid larva (Finnegan, S., 1945.

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Treatment and prevention of scabies.—Scabies is unlikely to be spread by blankets, but may be passed on in underclothes. Lack of washing facilities aid in its dissemination. "Norwegian scabies" is a severe type accompanied by profuse crusting and pustulation, as is often encountered in lepers. In West Africa it is often known as "craw-craw." The objection to sulphur ointments, which formerly were extensively used in treatment, is liability to sulphur dermatitis.

Kathiolan, a Danish preparation, is active and was used in the British Navy. *Proscabin* (Kissmeyer, 1937) and *Ascabiol* consist of a lotion of equal parts of benzyl benzoate, industrial spirit and soft soap. An aqueous solution is found by Mellanby to be more effective, though apt to cause dermatitis. The treatment is effected in forty-five minutes, without damage to the skin, and is inexpensive. The whole body is anointed with soft soap and the patient soaks in a warm bath (100° F.) for ten minutes. Using a brush of pigs' bristles, the body is brushed with 1½ oz. of the lotion. A second course is taken next day. The introduction of this method was an important advance, particularly for large numbers; it is rapid and simple. *Tetræthylthiuram mono-sulphide* (I.C.I.) in 5 per cent. solution is rubbed over the body, with the exception of the face and head, twice daily and does not cause dermatitis. It is cheap, clean and effective. The latest method of treatment consists of ½ per cent. *gammexane* (B.H.C.) in vanishing cream. One application is said to suffice.

DEMODEX FOLLICULORUM var. hominis (Simon, 1842) (Fig. 370)

Family: Demodecidae.

Genus: *Demodex*.

This mite is found in sebaceous glands and hair follicles, and is universally distributed. Usually it produces no symptoms, but it may give rise to dermatitis, and some species in animals to mange. A minute degenerate acarid, 0.3–0.4 mm. in length, it is not found in infants. Its structure is primitive. The head is provided with elongated rostrum. The female lays heart-shaped eggs (60–80 μ by 40–50 μ), from which hexapod larvæ develop. All the stages of development are passed within the follicles. The mature parasites migrate over the skin. To demonstrate them, sebum, expressed from the mouth of the sebaceous glands, or comedones, is examined with a drop of xylol. This parasite may give rise to a chronic dry erythema with follicular scaling. An ointment containing beta-naphthol and sublimed sulphur is said to be specific.



Pediculoides and Mites.—*Pediculoides ventricosus*, Fig. 370.—*Demodex folliculorum*. $\times 100$. (After Brumpt.)
found in cotton and cereals, usually feeds on caterpillars. In dock labourers and others handling cotton and crops it gives rise to dermatitis. The abdomen of the pregnant female is swollen with eggs like that of a miniature chigger; in it the eggs hatch and the young complete their development. Treatment is by carbolic lotion. (See p. 676.)

Tyroglyphus mites are found in cheese, flour and sugar, and cause copra itch or grocer's itch. The dermatitis may also be partially due to food sensitization.

Family: Trombidiidae.

Genus: *Trombicula*.

These are small, orange-red, "velvet mites," predaceous on their own kind, and on other insects and on plants. The larvæ resemble minute larval ticks,

but bear bristles on their back. The harvest-mite, the larva of *Trombicula autumnalis*, is small (0.5 mm.), just visible to the naked eye; it hatches out from eggs laid on the ground. These mites are normally parasitic on moles and hares; they live a few days on man, causing intense itching points with purpuric blotches. Inunction with dibutyl phthalate (*see* p. 234) is now used as preventive and cure.

Trombicula larvæ live on various plants and parasitise many animals and man. They abound in late spring, summer and autumn. The legs above the shoe tops are commonly attacked; less frequently the belt line.

The bite is inflicted in a curious manner, assisted by the secretion of the organism of a salivary substance which forms a tubular structure called a "histosiphon, or stylostome, extending through the skin of the host. The cutaneous reaction takes the form of an erythematous macule which becomes a papule in a few hours, surrounded by an erythematous halo.

The sudden appearance of severe pruritic bites in a person who has walked through grass suggests the presence of these mites.

Eutrombicula batatas (*Trombidium irritans*), the "chigger mite" of America is widely distributed, from Long Island and California to Mexico. In Florida the species is *E. alfreddugessi*. The larvæ attach themselves to the skin, but do not burrow in; secondary infection is produced by scratching. Local application of kerosene or 95 per cent. alcohol is curative. Dusting the clothes with flowers of sulphur is preventive. In Mexico *Neoschongastia nunezi* produces an irritating inepetiginous rash. Similar mites occur all over the world; the adult stages, known as "money spiders," are non-parasitic. *Schongastia indica* is the commonest mite parasite of rats of Java and it is believed to transmit rickettsiæ to them. Of medical interest are *Trombicula akamushi*, *T. schüffneri*, *T. deliensis*, *T. pallida*, *T. intermedia* and *T. scutellaris* and *T. hirsti*, "Kedani mites," the larval stages (*microtrombidium*) of which carry rickettsiæ of "scrub typhus" (Figs. 369, 371, 372). The hexapod larvæ live on the ears of the field-vole (*Microtus*) and the house-rat of Formosa (*R. rattus rufescens*), whilst other rodents may act as reservoirs. The mites attack men working in fields, producing a local necrotic ulcer. In Malaya workers engaged in weeding palm plantations: in the Dutch East Indies labourers clearing jungle are especially affected. These mites do not suck blood, but when firmly attached, inject a digestive fluid which is a proteolytic ferment. This fluid dissolves the tissues so that the resulting liquid may be utilized. The skin of the host becomes hardened, and a tube (stylostome) is formed in which the mite lies and where it continues to imbibe the fluid until it is replete. Then it retreats and drops to the ground. The reaction of this digestive fluid causes the bite to itch. The tube represents a reaction of the host to the secretions of the mite.

Although *T. akamushi* and *T. scutellaris* in Japan, *T. deliensis*, are the only proved vectors of *Rickettsia akamushi*, some 100 new species have been discovered since 1940. The chief reservoirs of infection of the mite-borne as well as of the tick-borne fevers of the typhus group are believed to be these arthropod vectors. The vertebrate hosts are now regarded as being merely transitory reservoirs. In Malacca, tomb bats, *Taphozous melanopogon*, are found infested with *T. deliensis*.

The adult form (*Trombicula*) (Fig. 372) is characterized by having spiracular openings of the tracheate system at the side of the beak (*capitulum*). It lives in soil and measures 0.9 mm. by 0.5 mm. It is pale grey or red, with rudimentary eyes, four pairs of legs, the anterior pair stout, situated on the anterior part of the cephalothorax parallel to the pedipalps. On the ventral surface are two pairs of suckers close to the genital orifice and anus. The *Trombicula* feed on insect eggs. They deposit their own eggs in late spring or early autumn in loose top

soil under leaves in damp places. The hexapod larvæ hatch in three weeks (measuring 0.32–0.43 mm. in length). They remain attached to their mammalian host, feeding for 3–4 days. They then drop to the ground and in 5–6 days moult and produce an eight-legged nymph. The infection of rickettsiæ by *Trombicula* may be hereditary. The larva (*microtrombidium*, or *leptotrombicula*) (0.4 mm. by 0.25 mm.) resembles that of the harvest mite, with its stout legs, pedipalpi and body, including the legs, covered with minute plumose hairs. The cephalothorax bears a conspicuous pair of red eyes. The nymph has a peculiar figure-of-eight shape, with abdominal constriction, and measures 0.65 mm. In due season it moults and becomes adult. Audy has described *Laurentella*, a new subgenus of 22 species in Oriental and Australian regions, of which one, *L* (or *Euschöngastia*) *indica*, is a widespread species and common as a commensal on rats in urban areas. *L. audyi* is dominant as a free-living organism on mammals of Malaya and Borneo. *Tetranychus molestissimus* is a mite which may cause "*larva migrans*" (see p. 836). This belongs to a group known as "red spiders," which infest vegetation and are well known as the "Bicho

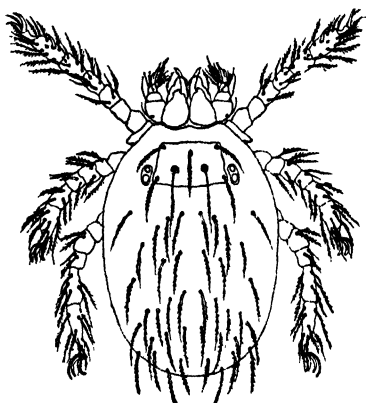


Fig. 371.—Larva of *Trombicula akamushi*. $\times 80$. (After Hirst, "*Journ. Economic Biol.*")

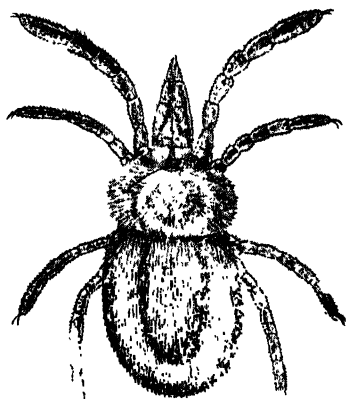


Fig. 372.—*Trombicula akamushi*: full-grown imago. $\times 35$. (After Mizajima and Okumura.)

Colorado" of South America. Persons employed in picking hops often complain of the itching produced by it.

For critical review of acari as transmitting agents, see S. Finnegan (1946), B.M. (Nat. Hist.) Economic Series, No. 16.

Superfamily: Ixodoidea (Ticks)

Ticks are cosmopolitan, and important carriers of disease. These large, blood-sucking Acarina are larger editions of mites. With the exception of *Argas* and *Ornithodoros*, they rarely attack man voluntarily in their adult stage. The females are invariably larger than the males. The shell is often highly ornamented, and has four pairs of segmented legs, and a single spiracle on each side between the third and fourth legs. The males never gorge themselves on blood to the same extent as the females. A specific distinction of this genus is the series of toothlike lumps on the protarsus of the first pair of legs. When they are gorged the posterior end expands. Ticks are divided into ARGASIDÆ (soft), and IXODIDÆ (hard). In the former there is no shield, the mouth parts are not visible from above, and there are no festoons. All lay shiny,

spherical eggs in enormous numbers—up to 5,000. The genital pore is situated in the middle line on the ventral surface, not far behind the capitulum. The excretory organs, or Malpighian glands, open into the hind gut and the coxa glands, which open on the front coxæ. These hatch into hexapod larvæ, which become octopod nymphs, three series of which usually develop before the adult stage is reached. All are endowed with a phenomenal capacity for fasting—some for 4–5 years.

Argasidæ live apart from their host, in burrows or crevices, and have the habits of a bug. Adult ixodidæ attach themselves to the host, and drop off when gorged; and after fertilization the male dies. In some species—*Margaropus*—the metamorphosis from larva to nymph, and from nymph to adult takes place on the same host; in others—*Hæmaphysalis*—the tick drops off before each moult, to find a new host three times in its life.

Family: Argasidæ (Soft Ticks)

GENUS ORNITHODORUS contains 20–30 species

Ornithodoros moubata (Murray 1877, Fig. 38, p. 176)

This tick is widely distributed in Central Africa. The body is rounded and manumillated and the legs tuberculated. The integument is greenish-brown, hard and leathery, marked above and below with symmetrically-arranged grooves, and numerous hard, shiny trabeculations. The carapace contains no "eyes." The females (12–14 mm.) are larger than the males (8 mm. by 7 mm.) and moult frequently. The habits resemble those of the bed-bug, and they live in native huts, thatched roofs, and cracks in floors and walls, emerging at night to suck the blood of man and beast, and in doing so inject also an anticoagulant and analgesic. *O. moubata* is found in burrows excavated by ant-eaters and porcupines, associated with wart-hogs, far from human habitations in Kenya and there they breed in large numbers (Heisch). The presence of these ticks is not consistently associated with relapsing fever. Three forms are now recognized which feed on man, chicken and wart-hog respectively. In Kenya, in the Digo district, where ticks are very numerous, but relapsing fever is infrequent, the ticks have micro-environmental conditions of hot and moist (relative humidity of 77 per cent.). Man-feeders are more characteristic of cooler, wet climates. It feeds slowly and cannot abstract much blood, except from a sleeping host, and is important as a vector of relapsing fever (*Spirochæta duttoni*). Spirochætes pass through the gut wall, and small infective forms arise in the body cavity and settle in various tissues, especially the ovaries, but not in the salivary glands. Spirochætal infection is transmitted in a hereditary manner, and the organisms have been found in the eggs. If the tick is allowed to feed for a few minutes, infection is not contracted, but fluid which contains the spirochætes is passed *via* the anus and coxal glands at the base of the second pair of legs, soon after the tick begins to feed. After about 10 minutes the whole surface of the tick becomes wet and the organisms enter the skin through the bite-wound. Eggs are laid in batches of 50–100 and the fertility of the female is favoured by liberal feeding. They hatch in 20 days and the larval stage is practically absent. On the thirteenth day the egg-shell splits, and about the same time the skin of the contained larva splits also, and an eight-legged nymph emerges, throwing off simultaneously both egg-shell and larval skin. There are several nymph stages, the largest of which may equal the adult in size.

O. moubata is common on travel routes. Rest-houses are always most infested, and ticks may be carried long distances in mats and bedding. Natives in parts of Africa, and the Boers, try to protect themselves by plastering their huts with mud and cow-dung and by frequently smoking them. Pyrethrum powder is a valuable preventive. This tick is comparatively resistant to DDT, but can

be killed easily by BHC at 1.25 grm./ft. in dusting the floors of houses, etc. The tick is difficult to dislodge and burning may not completely eradicate it. Old camping sites and native houses are to be avoided, and Europeans must never sleep on the floor.

In certain parts of Africa, Abyssinia and Somaliland *O. moubata* is overlapped by *O. savignyi* (Audouin, 1827), which prefers market-places and cattle byres in the vicinity of wells. It is distinguished by having eyes, larger processes on its legs and more minutely pitted dorsal surface. It can transmit *S. duttoni* (in the laboratory) but its exact rôle under natural conditions is doubtful, though suspected in Somaliland. It has been reported from Northern Nigeria, Egypt, the Sudan, East Africa, India and Arabia.

O. lahorensis (Newman, 1908), resembles *O. moubata* and has an anterior projecting hood. The adult lives in cracks of native houses and walls in Persia and North India. The nymphal stages are passed on sheep. It is suspected of carrying relapsing fever (see p. 170).

O. tholozani (Birula, 1895), syn. *O. papillipes*, the "Persian bug," is widely distributed in Palestine, Persia, India and Turkmenistan. In nature it is found in porcupine and jerboa burrows. The male is 4-6 mm. in length, the female 8-9 mm. It transmits *Spirochaeta persica* (see p. 172) and on biting injects an analgesic substance. Other species in Asia are *O. asperus* and *O. tartakowskyi*.

O. talaje (Guerin-Ménéville, 1849) resembles *O. venezuelensis*, and is found from Mexico to Paraguay. The female measures 5-6 mm. by 3-4 mm. It transmits *S. venezuelensis* (see p. 172 and Table II). *O. turicata* is also a vector from the same region with similar habits.

O. venezuelensis syn. *O. rudis* (Brumpt, 1921) is related to the foregoing, and found in Venezuela and Colombia at the higher altitudes, 3,000-5,000 ft. The female is larger than the male (5-6 mm. by 3-4 mm.). It lives in the walls of native huts in company with bed-bugs, and is very voracious. Eggs are laid in batches of 50-100. Hexapod larvæ, on emerging, feed actively within a few hours on mammalian blood. The nymphs feed without undergoing ecdysis, as in *O. talaje*, but thereafter they moult after each feed, becoming adult at the fourth. This tick conveys relapsing fever in the districts in which it occurs.

O. hermsi (Wheeler, Herms and Meyer, 1935) is a small ovoid species, sandy-coloured when not engorged. The female (5 mm. by 3.1 mm.) resembles the male (3.8 mm. by 2.4 mm.). It differs from *O. talaje* in minor details and in the smaller size of the male. It is found in the burrows of many rodents and in chipmunk's nests, at an elevation of 4,000-7,000 ft. near Big Bear Lake, San Bernardino County, California. It transmits *S. turicata* in California and Nevada, though tick-transmitted relapsing fever has now been reported from Colorado, California, Texas, Arizona, Nevada, Kansas, New Mexico, Washington and Montana.

O. turicata (Duges) is closely allied to the foregoing and is found in Mexico, Texas, Arizona, and possibly Kansas. Normally it lives on goats, sheep, foxes and rabbits.

O. erraticus (Lucas, 1849), syn. *O. maroccanus* (Velu, 1919), under natural conditions, lives in burrows far from human habitations. In Morocco it inhabits piggeries. In Senegal and Dakar it transmits *Spirochaeta duttoni* (syn. *S. crociduræ*), and in Spain and Morocco *S. hispanica*, in the hexapod larval stage. (See p. 172.)

O. normandi (Larousse) is found in Tunisia where it transmits *Spirochaeta normandi*, a parasite of gerbils (*Meriones shawi*).

Argas persicus (Fisher, 1824) and *A. miniatus* (Koch, 1844) are common in Northern and Eastern Persia, Syria, Turkestan, Russia, China, Algeria,

South Africa, North and South America, West Indies, Western Australia and Queensland, attacking poultry and man. They live in old houses, in cracks of the walls and floors. Normally they transmit *S. gallinarum* of fowls and ducks.

Family: Ixodidae (Hard Ticks)

Genera *Rhipicephalus*, *Dermacentor*, *Hæmaphysalis*, *Amblyomma*, etc.

There are 12 genera, all parasitic on mammals. All species of ixodid ticks pass through four stages—egg, larva, nymph and adult. They may have one or multiple hosts. The eggs are deposited on the ground where they hatch and give rise to hexapod larvæ which soon seek a blood meal. In the case of multiple host-ticks the engorged larvæ drop from the host after several days of feeding and seek a cool place where they remain till moulting takes place. The resulting octopod nymphs then feed on a second host, again drop to the ground and await moulting. The ticks emerge from the second moult as adult males and females. An interval of ten days is required for engorgement of the female, during which time mating takes place. The life-cycle normally extends from a few weeks up to ten or more years. After egg-laying is complete, the female dies. They lay eggs in enormous numbers, and the larvæ wait in herbage for their hosts. The chief are *Rhipicephalus* and *Dermacentor*. The former is usually brownish with an angulated basis capituli; the latter is highly ornamented and the basis rounded. Some feed and drop off: others have different hosts (cattle, rabbit, etc.); others, again, have different hosts at different stages. Debility is produced by multiple bites and secondary infections. "*Tick paralysis*" (see p. 833) is a toxic manifestation from the saliva when the tick has been attached for several days in the region of the head and neck. Coma, respiratory paralysis and death may ensue. In other cases the hypostome, plunged into the skin, may break the capitulum which, being left behind, gives rise to a septic focus.

Rhipicephalus sanguineus (Latreille, 1804) is a brown cosmopolitan species in the tropics, present throughout all months of the year. It is peculiar to the dog, in association with which the whole cycle is completed. Each individual normally has three hosts, one for each of the larval, nymphal and adult stages. The female engorges with blood and then immediately separates from the dog and lays 1,000–3,000 brown eggs which hatch at 25° C.; the larvæ attach themselves to a new host. At 15–20° C. they can live three to four months. This species transmits the rickettsia of typhus in Texas, South America and South Africa, "*fièvre boutonneuse*" of Marseilles, and also conveys canine piroplasmosis.

R. appendiculatus closely resembles the foregoing. The larval forms transmit the rickettsia of tick typhus in South Africa.

Hæmaphysalis leachi (Audouin, 1827) does not readily attack man. Its larval and nymphal stages are spent on carnivora, quitting the host at each stage. It is the active carrier of canine piroplasmosis in South Africa and has been incriminated there as a vector of typhus also.

H. humerosa, an Australian species, has been found by Derrick to transmit the rickettsia of Q fever (*C. burneti*) to man and parasitizes the bandicoot (*Isodon torosus*).

Amblyomma americanum (Linn., 1758), known as the "Lone star" tick, from the bright spot on the carapace of the female, is important as the vector of Rocky Mountain and "Bullis" fever in Texas, where it is abundant. Recently the pocket-gopher (a small rodent) which is parasitized by this tick has been found to constitute the reservoir of *Rickettsia rickettsii*. Found throughout North America and Brazil, it infests dogs, cattle and fowls. The larvæ frequently attack man and live in scrub and high grass.

A. hebraeum (Koch), an African species, is widely distributed on lizards and

birds, and occasionally attacks man. It has three hosts of the same species. The female may lay as many as 20,000 eggs and transmit the rickettsia of "tick-bite" fever in South Africa.

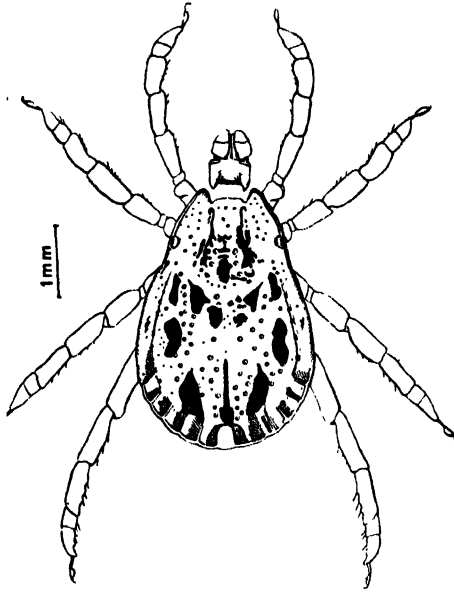


Fig. 373.—*Dermacentor andersoni*, ♂. (Nuttall.)

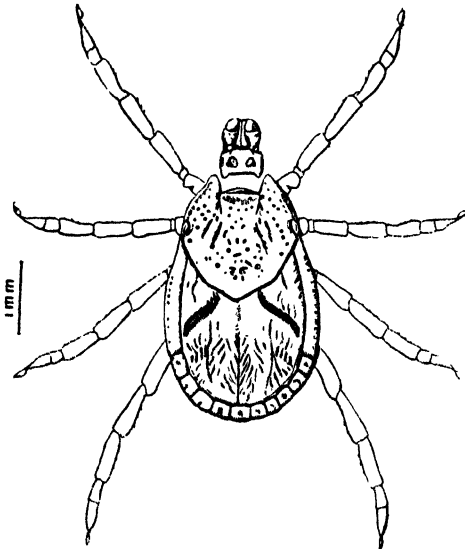


Fig. 374.—*Dermacentor andersoni*, ♀. (Nuttall.)

A. cajennense (Koch, 1844) is a large tick found in America from Texas to the Argentine. The males are adorned with a carapace of silvery design. The natural host is the peccary. It transmits the rickettsia of typhus in São Paulo, and, under laboratory conditions, that of Rocky Mountain fever.

Dermacentor andersoni (Stiles, 1908), syn. *D. venustus* (Banks, 1897), is an important carrier of Rocky Mountain fever in the Western United States, where it is known as the wood-tick. Primarily a rodent infection probably this is normally maintained by *Hæmaphysalis*, but rodents are also attacked by *Dermacentor*, so the infection "overflows" to man as in parallel cases of murine typhus. Tularemia (p. 277) is also occasionally transmitted. Abundant in the Rocky Mountains the adults appear during the summer, parasitic on horses, big game and other wild animals, and frequently on man (Figs. 373, 374). Larvæ and nymphs occur on small rodents and ground squirrels. The female, when engorged, deposits 5,000-7,000 eggs four to six days after quitting the host. Hexapod larvæ appear on the sixteenth day and in two to eight days engorge. After the larva has fallen to the ground and moulted, the nymph produced can survive for 300 days and, after itself feeding, falls to the ground and moults. Fully developed males and females can fast two years. After attaching themselves to a mammalian host they copulate in four days. The males remain attached, the females fall to the ground and deposit their eggs. Under natural conditions the cycle takes two years.

D. variabilis (Say, 1821), the dog-tick, is widely distributed in North America, most abundantly on the Atlantic coast. In its immature stages it feeds on small rodents, especially mice; the adults attack dogs and other large animals. It resembles the foregoing. It is the principal vector of spotted fever (typhus) in Central and Eastern United States (see p. 212) and may cause paralysis in dogs. Arsenical dipping of sheep and goats acts as a control, whilst the rodents should be killed off.

Ixodophagus is a small wasp parasite of ticks found in Europe and introduced into America to combat dermacentor.

A vaccine made by grinding up infected ticks (*D. variabilis* and *andersoni*) was once employed as a prophylactic against Rocky Mountain spotted fever. It protects for about one year.

FAMILY: LINGUATULIDÆ

Class: Pentosomida.

Family: Linguatulidæ.

The linguatulids, pentastomes or "tongue worms," are degenerate arachnids with an annulated body, which gives them a rough resemblance to tape-worms.

Genus: *Linguatula*.

LINGUATULA SERRATA (Frohlich, 1789) (Fig. 375)

This is found in Southern Germany, Switzerland and Brazil.

This linguatula (Fig. 375) in its adult state inhabits the nasal cavities of dogs, wolves, and foxes; rarely of sheep or goats. The larvæ are met with frequently in the mesenteric glands of domestic animals, as well as in rabbits and hares, and were found by Zenker in 4.6 per cent. of human livers, but appear to cause no symptoms. In Brazil it has been recorded as an intestinal parasite. A pulmonary infection resembling tuberculosis has been recorded in man in Dallas, Texas. The infection seems to be acquired through eating raw vegetables contaminated by nasal secretions of dogs.

Characters.—The body of the parasite is somewhat pear-shaped, flattened, and transversely striated with about 90 rings; the mouth is roughly quadrangular and surrounded by hooks. The intestine is simple. The male is white, 18–20 mm. long, and measures 3 mm. broad anteriorly, 0.5 mm. posteriorly. The female, 8–10 cm. in length, is grey, but may be brown when packed with eggs; anteriorly she measures 8–10 mm. broad: posteriorly 2 mm.

The eggs are ovoid, and 90 μ in length by 70 μ in breadth. They contain ripe embryos when deposited by the female, and pass out with nasal mucus to become

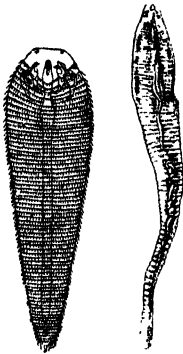


Fig. 375.—*Linguatula serrata*.
(After Brumpt.)

1, Larval form ($\times 6$); 2, mature form (nat. size)

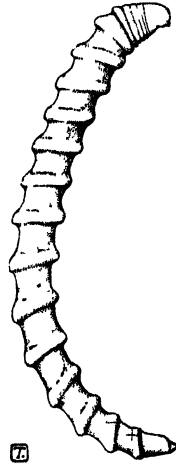


Fig. 376.—*Porocephalus armillatus*.
Nat. size. (After Sambon.)

attached to grass and other herbs; they are then ingested by the definitive host, penetrate the intestinal coats, and enter the viscera, the liver, lung, mesenteric glands, kidney, etc. The larva, having grown to 5–6 mm. in length, encysts, and is ingested by various carnivora, then escapes from the cyst, falls into the peritoneal cavity and even into the intestinal lumen, and in this manner reaches the adult stage in the nasal cavities of the same host.

Genus: *Porocephalus*.

POROCEPHALUS ARMILLATUS (Wyman, 1848)

Synonym.—*Armillifer armillatus* (Fig. 376).

P. armillatus occasionally infects humans, especially negroes in Central Africa. It has been recorded from Java (Salm), Manila, Sumatra, and China.

Characters.—The adult parasite is found in pythons and other snakes; the nymphal form in the lion, mandrill, giraffe and African hedgehog. The arachnid is vermiform, yellowish and translucent. The anterior part is cylindrical, the posterior tapering into a blunt-pointed cone. In the male there are 17—in the female 18–22—prominent opaque rings (each 1–2 mm.). The male is 3–5 cm. long, the female 9–12 cm. There is no clear separation between the cephalothorax and the abdomen. The mouth opening is capped by two prominent papillæ on the ventral surface, lipped by a chitinous ring. On either side are two protractile chitinous rings; the anus is terminal. The genital orifice of the male lies at the anterior end of the abdomen; that of the female opens in the middle of the

ventral surface of the caudal cone. The female is oviparous. The eggs are broadly elliptical, double-shelled, and measure $108\ \mu$ by $80\ \mu$.

The nymph lies coiled within the cyst, with its ventral surface corresponding to the convexity of the curve. In shape and structure it resembles the adult. Calcification may take place in the liver and other organs.

The life-history of *P. armillatus* is similar to that of *L. serrata*. There is no doubt about the gravity of a heavy infection, when the parasites are migrating in the intermediary host. Broden and Rodhain have found them in 33 out of 133 post-mortems on the Belgian Congo; a large number were within the lumen of the small intestine, and many encysted in the lungs. Manuwa has (1935) reported an acute and fatal case in Nigeria. At autopsy numerous nymphs were found in radicles of the portal vein and attached to the mesentery. When cretified, the parasites may be demonstrated by skiagraphy as in Low's case (1936). Otherwise, diagnosis during life is impossible. Acute abdominal symptoms may arise as in Gray's case (1954), caused by intussusception and invagination of Meckel diverticulum, by cystic tumours containing larval forms of *P. armillatus*. In oriental regions *P. armillatus* is replaced by *P. moniliformis*, which is also parasitic in pythons. It is more slender and has more rings. Two cases of infestation with *P. crotali* of the rattlesnake have been reported in U.S.A.

ORDER: DIPTERA

Class: Insecta

Family: Psychodidae

GENUS *Phlebotomus* (SANDFLIES) (Figs. 377, 378)

Phlebotomi, of which a large number are known, are minute, hairy flies (1.5 to 2.5 mm.) which are readily recognized. The females only suck blood. The males suck up moisture from any available source. In some people the bites cause local disturbance; in others, none. Sandflies carry sandfly fever (p. 23), oriental sore, espundia and kala-azar (pp. 131, 154, 164).

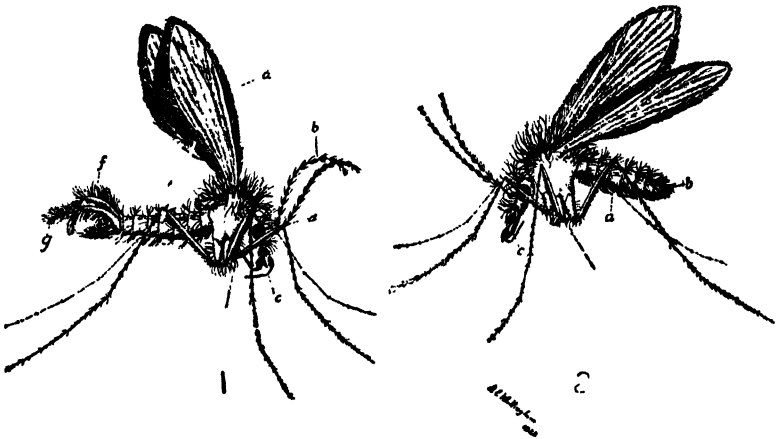


Fig. 377.—*Phlebotomus papatasi*. $\times 10$.

(After Whittingham, "Brit. Med. Journ.")

1. Fully developed male imago. *a*, Hairy wings; *b*, antennæ; *c*, labial palps; *d*, eye; *e*, halteres, *f*, claspers; *g*, genital spines.
2. Fully developed female imago. Body hairs arranged in tufts; abdomen (*a*) spindle-shaped, *b*, ovipositors; *c*, proboscis.

P. verrucarum and also *P. noguchii* (Shannon) transmit *Bartonella bacilliformis* of Oroya fever (Townsend), and have a wide distribution. *P. papatasi*, which extends north to Paris and transmits sandfly fever, is widespread through Southern Europe, North and East Africa, Java and India. The body is covered with long hairs, the counterpart of scales. The antennæ have sixteen joints; the proboscis is short and contains the piercing organs. The wings are hairy, pointed and folded roof-wise on the back; venation is distinctly seen on removal of the scales; the legs are long and slender. The abdomen of the female is spindle-shaped and provided with small claspers, but the male has two pairs of appendages—the upper and lower claspers—and various other structures known as the intromittent organ, the submedian lamellæ, and the intermediate appendages.

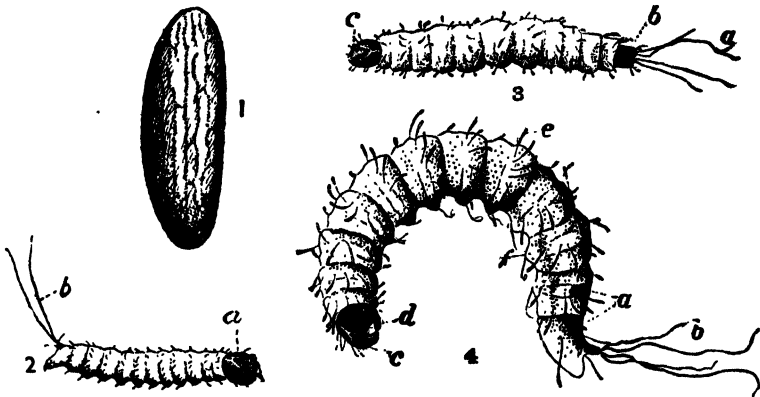


Fig. 378.—Life-history of *Phlebotomus papatasi*.

(After Whittingham, Brit. Med. J.)

1. Fertilized egg, seven days after oviposition. $\times 80$.
2. First stage of larval life, two days old. a, Head with Y-shaped mark and egg-tooth; b, caudal bristles. $\times 40$.
3. Third stage of larval life (dorsal view), thirteen days old. a, Caudal bristles; b, last segment; c, antennæ. $\times 20$.
4. Fourth stage, twenty-two days old. a, Last segment; b, caudal bristles; c, mandibles; d, labial plate; e, body hairs; f, false legs. $\times 20$.

Whilst feeding, sandflies are easily disturbed. The stout rostrum is thrust downwards whilst the maxillary palpi diverge and within a minute blood enters the stomach. Sandflies are abundant in the drier portions of the tropics and subtropics, but occur also in wet parts. They fly by night, and shelter in dark corners during the day. The flight is feeble, more like a hop than flight. Their range is usually not more than fifty yards from the breeding places, and they do not rise far above ground level. The maximal vertical distance is 70 feet. Many species do not attack man, but feed normally on the blood of animals such as field mice, even lizards. In the hot deserts of Central Asia sandflies are common in the burrows of gerbils, ground squirrels and tortoises, as well as those of wolves, jackals and foxes. The sandflies are abundant in April and the early part of May but are not seen again till next spring (Petrishcheva).

Life-history.—Considerable moisture is necessary to induce oviposition. The eggs (0.385 by 0.12 mm.), laid singly, are black, like those of *Aedes*, and reticulated. They are laid amongst rubble in caves or in cracks of masonry. The breeding places vary in different parts of the world: in Peru, rubble and loose earth; in Egypt, damp cracks in sand, and in India *P. argentipes* breeds in broken patches in paved floors, where the soil is contaminated by the faeces

of fowls, cows and goats. When organic matter is present, the eggs hatch in six to nine days into twelve-segmented caterpillar-like larvæ with long dorsal bristles on the terminal segment (Fig. 378, 2). Each bears a number of spines arranged in a transverse row, and the larva progresses by slow, undulatory movements, feeding on decaying nitrogenous material, moulds, dejecta of lizards and the bodies of defunct parent flies. The duration of the larval stages varies up to four weeks. There are four distinct stages with a complete moult between each (Whittingham). According to Roubaud, sandflies are heterodynamic, and do not all develop in same manner, so that some individuals remain as larvæ for considerable periods and hibernation takes place in the larval state. Moisture is necessary; in deserts it is probably obtained from water of condensation. The pupa stage lasts about nine days. It is ochreous-buff and has thoracic appendages free from the body. The integument is covered with minute squames, and there are small spines on the sides of the thorax and abdomen. The imago hatches out in the early hours of the morning when atmospheric humidity is high. Adults are crepuscular, nocturnal and active on warm still nights, repelled by sunlight but attracted by artificial light, but some sandflies feed voraciously during the daytime.

The incidence of *P. papatasi* in Mediterranean sandfly fever is definitely related to the number of breeding places. The virus can be transmitted by the bite of the progeny of infected flies, which is probably due to the larvæ eating the bodies and faeces of adults. In Algeria it is common in autumn; oriental sores occur about six weeks later. In India *P. sergenti* transmits *Leishmania tropica* and *P. argentipes* transmits *L. donovani* (for proof, see p. 135). In kala-azar epidemics in Bengal, 1920-30, the incidence was always greatest in those living on ground floors, thus corresponding to the habits of the sandfly.

In China there is agreement between kala-azar, *P. major* and *P. chinensis* and in Italy between this disease and *P. perniciosus* (96.8 per cent. of which became infected after feeding on infected hamsters).

The following is a brief description of some better known species:—

P. argentipes.—Dark brown, medium-sized, 2.3-2.8 mm. long. On the thorax the dorsum is black, sides light yellow. The wings are broader than in most species. The tarsi are white. Not found outside India it is most prevalent in Bengal and Assam during and after the monsoon.

P. major var. *chinensis*.—Colour variable, dull greyish to bright yellow. The abdominal hairs are more or less erect dorsally and are of a uniform golden grey. The disc of the wings has a bluish iridescence. The eyes are black and the legs darker than the abdomen, which is clothed with long recumbent hairs and has tufts of longer upright ones on the dorsal surfaces.

P. perniciosus.—The thorax may have dull red-brown spots which are arranged in a triangle. Occasionally a similar spot is present on the vertex of the head. The eyes are black, the thorax and coxæ pale, translucent and ochreous. The abdomen is similar and sometimes a pale smoky grey, and the hairs are pallid; the wings iridescent in a strong light with a distinct metallic lustre. The abdomen is densely hairy, the largest arising from the apical margin of the segment, but no distinct tufts as in *P. papatasi*.

Repellents.—Paraffin is effective, and oil of citronella is widely used. "Flit" and "Parquit" are pleasant and efficient if rubbed into the skin. Dibutyl-phthalate and DDT are now being employed (see p. 234). Sandfly nets are provided for troops.

The control of sandflies involves removal of rubble, provision of suitable houses and repair of masonry.

For preservation the insects should be placed in a web-like layer of teased cotton-wool, but must not be covered up.

FAMILY: CULICIDÆ (MOSQUITOES)

Mosquitoes are not confined to tropical regions; many species (including anopheles) are found even within the Arctic circle. The adult insects feed on vegetable juices; the males almost exclusively. The females of most species

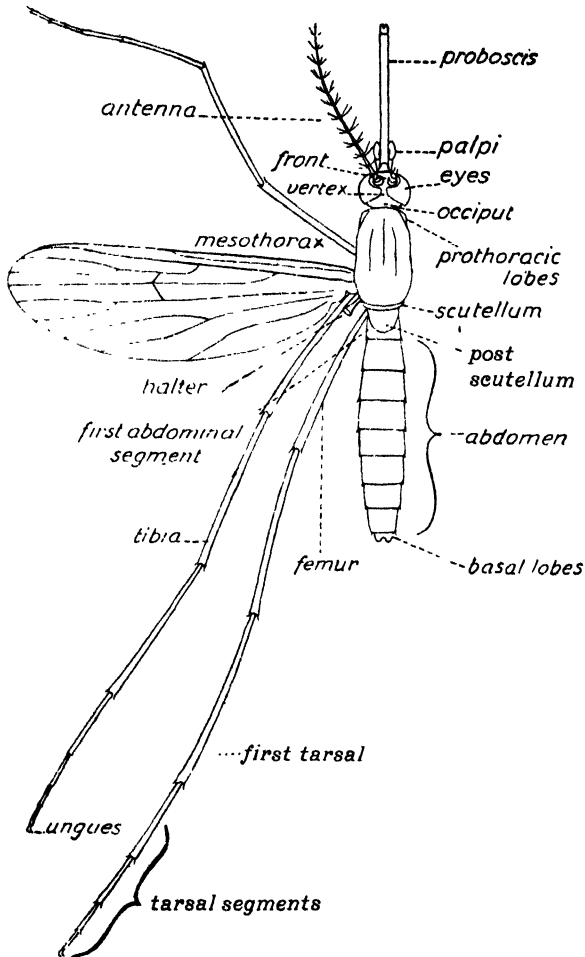


Fig. 379.—Female mosquito, to show anatomy.

suck the blood of mammals and birds. Many act as carriers of disease (Fig. 379). They lay eggs singly, in groups, or in boat-shaped masses. Hatching out depends upon temperature. In some species the eggs remain dormant throughout the winter, or in drought. In ordinary circumstances the larvæ

hatch out in two or three days, then feed upon organic matter suspended in water. They breathe in air through the respiratory siphon situated near their tails. The larval stage lasts from six days to several weeks, usually ten days. The final is the fourth.

The pupa is free and active for 2-4 days. It rests on the surface and an air-film develops around it. When it is swallowed this film expands and splits

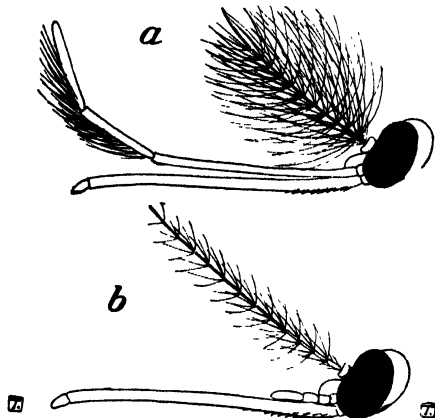


Fig. 380.—Heads of Culicini.

a, Male; b, female.

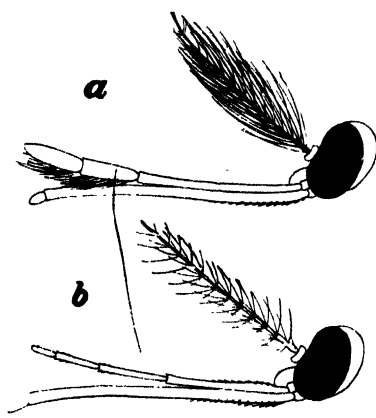


Fig. 381.—Heads of Anophelini.

a, Male; b, female.

the pupal case. When more air is swallowed, the mosquito works its way out. The abdomen is contracted, and blood is forced into the wings, which then expand. The mosquito rests $\frac{1}{4}$ – $\frac{1}{2}$ hour on its pupa case until its wings and body have hardened.

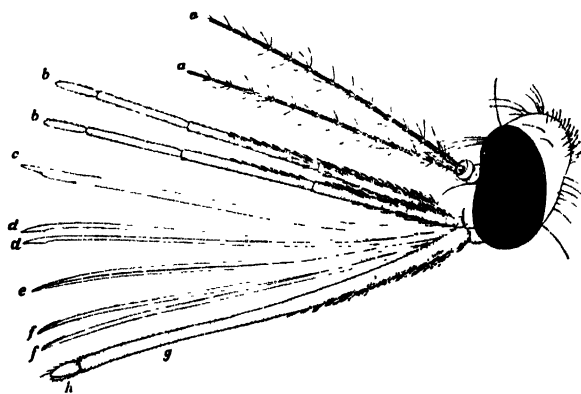


Fig. 382.—Mouth-parts of female mosquito.

a, a, Antennae; b, b, palpi; c, labrum-epipharynx; d, d, mandibles; e, hypopharynx; f, f, maxillae; g, labium; h, labella.

In Europe the whole process from egg to imago occupies about one month, but in the tropics seven to ten days. During colder weather development of the larva is temporarily suspended and the surviving adults, especially females, hibernate in dark and sheltered places. In this manner the species is carried

over the winter. In some varieties there is evidence that hibernation is carried out in the egg and larval stages. The life of an adult mosquito is variable, but some species, if supplied with suitable food, can live for several months.

Although most mosquitoes are singularly local, yet migrations are occasionally observed, and the insects are often transported great distances in ships, railway carriages or airplanes, and widely diffused. One or two species in most genera are domestic in anopheles, culex, theobaldia, etc. There are over a hundred species of *Aedes* and of these three only are domestic: others are jungle-dwellers. The majority are nocturnal.

Identification is necessary to recognize the structures by which they are classified. There are three recognizable divisions: head, thorax and abdomen. (Fig. 379). The head is rounded and attached to the thorax by a slender neck.

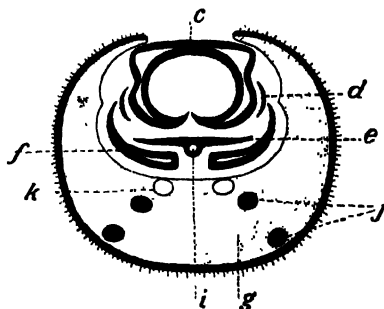


Fig. 383.—Section of mosquito's proboscis.

(Adapted from Nuttall and Shipley.)

c, Labrum-epipharynx; d, mandible; e, hypopharynx; f, maxillæ; g, labium; i, salivary duct; j, muscles; k, trachea.

It is provided with large eyes, antennæ and mouth parts. The antennæ (Figs. 379-381) are composed of fifteen segments. Each bears a whorl of hairs in the female, but in the male the hairs are profuse, giving a bristly appearance. The mouth parts consist of a proboscis in the female fitted for piercing and sucking. Externally, a chitinated labium (Fig. 382) encloses the other mouth parts, except the maxillary palpi, and ends distally in two pointed labellæ clothed with scales and hairs. The labrum is a hollow cylindrical tube with a narrow opening on the ventral surface. In the act of biting, the labellæ part and are applied to the surface of the skin, forming a sheath for the delicate piercing organs, and do not enter the wound made for obtaining blood. Within is the labrum-epipharynx, composed of two thin chitinous lamellæ imposed on each other, forming a V-shaped channel which is open on the ventral surface. This extends along the whole length of the labium and ends in a sharp point. Lying directly beneath the labrum-epipharynx, closing the ventral slit, is the hypopharynx, consisting of a thin, chitinous lamella, fitting closely to the ventral surface of the labrum-epipharynx, thus forming a tube through which blood is sucked. In the longitudinal chitinous thickening runs a very fine channel extending from base to tip of the hypopharynx; through this the salivary secretion is poured into the wound (Fig. 383). The mandibles are delicate chitinous structures at the side of the hypopharynx. The labium buckles in the act of biting, and the mouth parts emerge. Each of these tapers slightly towards the tip, ending in a sharp point. The maxillæ are more robustly constructed, but have the same general form, the tip is generally provided with a row of backward projecting teeth. The maxillary palpi consist of three to

In the male the mouth parts are greatly modified and not adapted for piercing. The maxillary palpi are elongated, extending beyond the tip of the proboscis, but the mandibles and maxillæ are greatly reduced and may be lacking altogether.

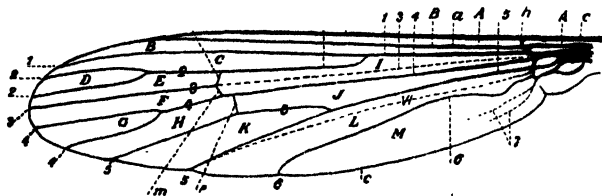


Fig. 384.—Wing of *Culex* (male), to illustrate terminology.

a, auxiliary vein; c, costa; 1-6, first to sixth longitudinal veins and branches; 7, seventh or false (unscaled) longitudinal vein; h, humeral transverse vein; m, middle transverse vein; p, posterior transverse vein; s, supernumerary transverse vein; A, costal cells; A', subcostal cells; C, marginal cells; D, anterior fork cell or first submarginal cell; E, second submarginal cell; F, first posterior cell; G, hinder fork or second posterior cell; I, first basal cell; J, second basal cell; K, anal cell; L, axillary cell; M, spurious cell; VI, unscaled vein between fifth and sixth longitudinal veins.

In the female anopheles the palpi are as long as the proboscis and usually closely applied, but in the male this feature is not nearly so marked. In both male anopheline and culicine mosquitoes the palpi are as long as the proboscis. The palpi of the male culicines are bushy, and the two terminal joints tend to turn upwards; those of the male anopheles are rather club-shaped.

The *thorax* is wedged-shaped: the sides form the pleura, whilst the apex bears the legs, and spiracles which are prominent black-rimmed apertures. The various sclerites composing the side of the thorax bear stiff *setæ* or hairs, arranged in definite groups. The scutellum is separated by a transverse suture from the mesonotum. In all genera, except anopheles, it is trilobate, and each lobe bears a group of stiff *setæ*. In anopheles the scutellum is arcuate. The region behind

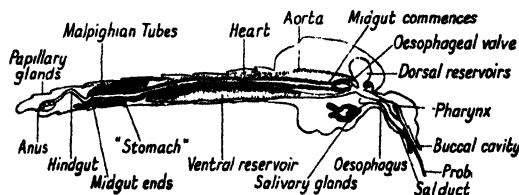


Fig. 385.—Longitudinal section of female mosquito to show anatomy.

the scutellum is known as postnotum and is generally nude. The wings are long and narrow; venation-bearing scales are characteristic (Fig. 384). Situated immediately posterior to the base of the wings is a pair of halteres or balancers, which are sense organs connected with flight. (Fig. 379).

The legs are long and slender, composed of coxa, trochanter, femur and tibia, and a tarsus of five joints, the last of which is long and slender, especially in the hind legs. The last tarsal joint bears a pair of claws (ungues), which vary greatly in size and shape, but those of the hind legs are generally smaller than those of others. The *abdomen* is nearly cylindrical, narrow and elongated, consisting of eleven segments. The first eight are quite similar, but the terminal

segments are modified for sexual purposes. The terminal segment in the female is pointed. The ninth is reduced, and in the intersegmental area between it and the eighth lies the opening of the reproductive organs. The tenth segment is greatly reduced and bears the basal lobes (cerci) and anal opening. The abdomen of the male is frequently longer than that of the female. The terminal segments are greatly modified and bear clasping organs. In the male the seventh and eighth segments undergo torsion through an arc of 180° after emergence from the pupa, with the result that the eighth tergite and those distal to it become ventrally situated, and the sternite dorsal.

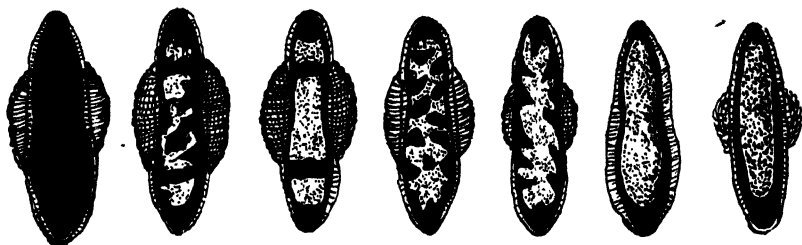


Fig. 386.—Eggs of the *Anopheles maculipennis* complex. (After P. G. Shute.)

1.	2.	3.	4.	5.	6.	7.
<i>Melanoon</i>	<i>Messeae</i>	<i>Typicus</i>	<i>Atroparvus</i>	<i>Labranchiae</i>	<i>Sacharovi</i> (<i>elutus</i>) (Summer)	<i>Ibid</i> (Spring & Autumn)

The main difference between 2 and 3 is that 2 has two "chevrons"; 6 has no floats, 5 very small and 4 medium. 1, 2 and 3 have large floats. 1 has about 20 ribs in the float without striations; 2 and 3 about 20 ribs with coarse striations; 5 has 10-12 ribs with striations.

The foregut and midgut are ectodermal, lined with chitin, continuous with the cuticle. Columnar epithelium lines the midgut. The entrance of the five Malpighian tubes marks the junction of hind and midguts. There are three salivary glands on each side. Various diverticula branch off from the gut (see Fig. 385).

Dissection of mosquito.—After chloroforming, the insect is placed on a slide in a drop of saline; the wings and legs are cut off. For dissection of the salivary glands one needle is applied behind the head and a second held horizontally on the thorax. The head is pulled forward, dragging out the salivary glands: this movement should be done in stages, with frequent jerks. Next the head is removed from the glands and the preparation covered with a coverslip. Examined under $\frac{1}{4}$ th lens, refractile sporozoites can be seen in a malaria infected anopheles. For dissection of the gut, the rectum is pressed up and down with pointed needle and then the body is cut through near the termination of the rectum. Gentle traction draws out the rectum and gut in a series of jerks. These are covered with a coverslip and examined. The tracery of fine black lines over the stomach denotes the tracheæ, and this feature can be used for focusing down with $\frac{1}{4}$ th lens in order to demonstrate malarial oöcysts.

SUBFAMILY: CULICINÆ

Tribe: Anophelini.

Genus: *Anopheles*.

The palpi in both sexes as long, or nearly as long, as the proboscis. The scutellum is rounded, without lobes, and the eggs are laid singly.

Anophelini were divided by Edwards into three genera: *Chagasia* (scutellum slightly trilobed), *Bironella* (scutellum evenly rounded, wing with stem of median fork wavy) and *Anopheles* (scutellum evenly rounded, wing with stem of median fork straight). The genus includes 160 species. The commoner kinds, whilst resting, hold the proboscis, head and abdomen nearly in a straight line, and give the appearance of a splinter lifted at an angle from a surface; exceptionally, as in *A. culicifacies*, the resting position adopted is more culex-like (Fig. 409). Usually the hum produced by these mosquitoes is low-pitched, almost inaudible unless close to the ear. Most of them are not strong fliers, and seek cover, even in a moderate breeze, yet dispersal flights may carry individuals ten or more miles from their breeding places. The flight range is 2-2.7 miles.

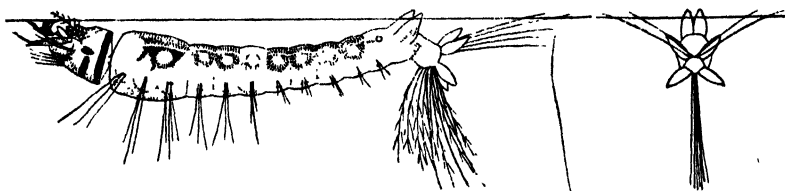


Fig. 387.—Larva of *Anopheles maculipennis* Meigen, showing breathing position at surface of water. (After Howard, "Bull. United States Dept. Agr.")

Fertilization of the female takes place directly upon emergence from the pupa. The males emerge first, and swarm over the breeding places awaiting the females; when the insects dart into a dancing mass, mating occurs. Most species require wide spaces for mating, rendering it difficult to propagate them in captivity. Over-wintering females are fertilized by the last brood of the males during autumn; the eggs are deposited soon after the spring dispersal flight. The

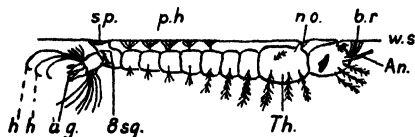


Fig. 388.—Larva of *Anopheles maculipennis* to show feeding position. (After J. F. Marshall.)

An, antenna; a.g., anal gills; br., mouth brush; h, h, hooked (grapnel) hairs; n. o., notched organ; p.h., palmate (float) hairs; s.p., spiracles; Th., thorax; w.s., water surface; 8 sg., 8th abdominal segment.

boat-shaped eggs (Fig. 386), with rare exception, having an investing membrane inflated laterally to form a pair of floats. They are laid singly on the surface of the water and hatch in two to three days. The larva during growth undergoes four moults. The cuticle is laid down by a single layer of epidermal cells, which form a new and folded cuticle, the larva inflating itself by swallowing water before the new cuticle hardens. The larva feeds on small floating particles swept into its mouth by two feeding brushes which can be folded under its head. When anopheles larvae lie on the surface, the dorsal aspect of the thorax and abdomen faces upwards, but the head is rotated 180° so that its ventral surface lies upwards (Fig. 388). Food consists of living organisms, bacteria and protozoa obtained beneath the surface. The head of the larva is complex: the central portion is known as the clypeus, the anterior plaque as the preclypeus. It has a pair of short antennae, eyes, a pair of feeding brushes, and preclypeal and clypeal hairs. The respiratory opening is composed of two dorsally placed

spiracles on the 8th abdominal segment. There is no respiratory syphon. (Fig. 387.)

The larva maintains itself on the surface in a horizontal position by a row of dorso-abdominal plaques, palmate hairs and a series of scales in rosette form on its back. The terminal segment is provided with four anal papillæ (gills), dorsal and ventral, and swimming brushes (Fig. 390). The gills have no respiratory function, but take up chlorides from the water. The eighth segment is adorned with a chitinous comb. Tracheæ run the length of the body with branches extending to all regions. Small glands secrete a waxy substance near the spiracles, which therefore cannot be wetted. (It is important to note this fact in oiling water to kill larvæ.) Respiration also takes place through the cuticle, but the oxygen intake from the water is not sufficient to maintain life, except when the temperature is low and metabolism is reduced. The pupæ are distinguished by the shape of the respiratory trumpets and by the presence of a paddle hair (Fig. 389).

The stages of metamorphosis are egg, larva, pupa and imago. The casting of successive larval skins is termed *ecdysis*. The larval stage is from hatching to

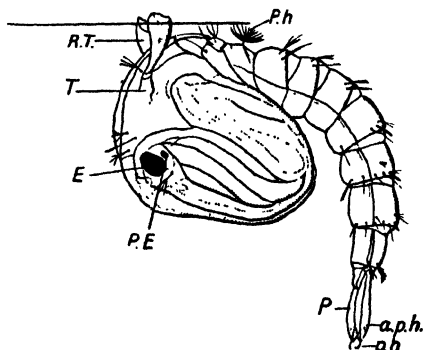


Fig. 389.—Pupa of *Anopheles maculipennis*. (After Marshall.)

E, eye; P, paddle; P.E., pupal eye; P.h., paddle hair; A.p.h., accessory paddle hair; R.T., respiratory trumpet; T, trachea leading to anterior thoracic spiracle.

the first ecdysis. In each stage the head remains unchanged. The fourth ecdysis determines the final larval stage (fourth stage larva) results in *pupation*, followed by emergence of the imago. The deposition of eggs is *oviposition*.

Gonotrophic cycle.—Fertilization is evidenced by packing the *spermatheca* with spermatozoa and as blood is digested so the ovaries enlarge. The complete cycle from feeding to oviposition completes the *gonotrophic cycle* and extends over a period of 2-3 or more days.

The blood meal may be obtained from man, cattle or other animals or birds. *Anthropophilic*, *Zoophilic* and *Neutrophilic* are terms which indicate preferences for feeding upon man, cattle or both indiscriminately. Where, owing to *host-preference*, there is a reduction of anopheles feeding on man, this is referred to as *animal deviation*.

Only the adult females are able to suck blood, but they do also feed on fruit juices in late summer when the grapes are ripe. The males feed on flower and fruit juices. The females can survive, but cannot lay eggs, on a diet of vegetable juices; this function needs a rich protein meal, and they usually suck blood at night, but times vary with the species, and in dark rooms they may feed during the daytime.

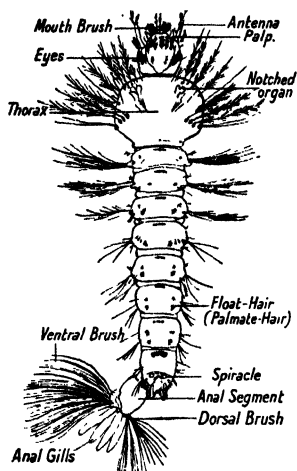


Fig. 390.—Larva of *Anopheles* (*A. maculipennis*) from above. (After Marshall.)

The anal segment is twisted round so as to display the dorsal and ventral brushes.

The capabilities of any particular species of anopheles to transmit malaria are regulated by a number of factors, such as the numbers present, whether the parasites of malaria can complete their development in the mosquito, anthropophilism (readiness to feed in nature on human blood), and whether the insects feed in the jungle or readily enter houses. Some species prefer swamps when breeding. The term "zoophilism" is employed when the insect is deviated by animals, i.e., cattle, as habitually happens with races of *A. maculipennis*. The nature of the vegetable food of the female is important, as some substances interfere with development of the malaria parasite. A species proved to be a natural carrier in one situation does not necessarily play an important part somewhere else, e.g., *A. aconitus* in Java. In North America *A. crucians* is found to be an efficient carrier when bred in brackish water. Again, *A. subpictus* (*rossii*), as a rule, plays little or no part in the transmission of malaria in India, but yet during an epidemic it may be found infected up to 8.6 per cent. in Java.

There is a striking correlation between the incidence of malaria and of anopheles as seen in the case of *A. punctulatus* complex which occurs on some islands in the South Pacific, but not on others. Where these species occur there is malaria; where they do not, there is none. (Rezeboom and Knight (1946), *J. Parasit.*, 32 (2), 95.) Nomenclature is a vexed question. A great many species have been renamed in recent years. In case of doubt recourse should be made to the *Index Insectorum* and the monumental publications of the British Museum by Edwards. For example, *Anopheles rossii*, one of the first *Anopheles* to be described and experimented upon by R. Ross, is now found to be the same as *A. subpictus*.

In making a malaria survey all adult female anophelines in and around the house should be collected and dissected to find out which species is infected. It is necessary to dissect several hundred insects and to examine the gut and salivary glands. An infection rate of 5 per cent. is usually heavy, though higher rates are recorded in Africa. Adults and larvæ should be identified to determine dangerous carriers. The locality should be studied for at least a complete year. Seasonal transmission is important; one species may be responsible in spring and another during the autumn.

Identification of the many diverse species of anopheles is specialized work. The following points are of specific importance: size, general colouration, colour of frontal tuft on the head (yellow or white), and character of the scales. (Fig. 391.) The distal half of the proboscis may be pale, the palpi may be smooth or shaggy, depending on the scales. The markings (banding) on palpi may be entirely dark or there may be pale bands. The general colouration of the thorax and scales on the mesonotum is helpful. The scales on the wings may be entirely dark, or may have four pale areas. The third vein may be entirely dark or pale. Pale spots may be present on the fringe opposite the various veins. Speckling, or banding, of the legs is an important point, and the presence or absence of lateral tufts or buttons of the large scales on the abdomen. In

scientific entomology, larval characters of the last stage, or fourth instar, are important as a basis of classification. These features are too intricate to be detailed here (see J. Smart, "Insects of Medical Importance"; British Museum Publications).

A. maculipennis (Fig. 392) has a wide distribution as a most important carrier of malaria. It is nocturnal in habits and is most active between midnight and 2 a.m. It indulges in a marriage flight and a constant change of resting place

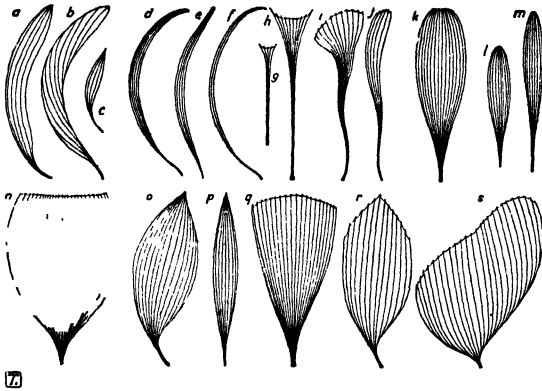


Fig. 391.—Graphic key to distinctions based on scale characters.

a, b, c, Narrow curved scales; d, e, f, hair-like curved scales; g, h, upright forked scales; i, j, long, twisted scales; k, large lanceolate scale; l, m, small narrow lanceolate scales; n, large expanded scale; o, p, spindle-shaped scale; q, broad flat scales; r, s, broad irregular scales.

appears indispensable to its existence, so that the anopheline population may become entirely changed within a few days.

Hackett and Missiroli showed that *A. maculipennis* is not a homogeneous species, but a collection of widespread varieties which may possibly represent species. Those generally accepted are:

A. maculipennis, Meigen, or *typicus*, which lays eggs with two simple bars; *A. m. messeæ*, Falleroni, which lays dark barred eggs; *A. m. melanoon*, Hackett, which lays uniformly black eggs; *A. m. atroparvus*, Van Thiel, which lays a dark grey and dappled egg; *A. m. labranchiæ*, Falleroni, which lays a light grey and dappled egg; and *A. m. sacharovi* (or *elutus*), Edwards, which lays a uniformly grey egg (Fig. 386).

These varieties are identified by the markings of the eggs and character of the floats, by the larval hairs, and by the external harpaginal spine of the adult male. Authorities are of the opinion that the egg-types provide a satisfactory method of dividing *A. maculipennis* (Fig. 392), but Ungureanu and Shute have demonstrated that the adults can be distinguished from one another by the different shapes of the wing scales. In *atroparvus* the scales are slender and taper gradually towards the tip; in *messeæ* they are

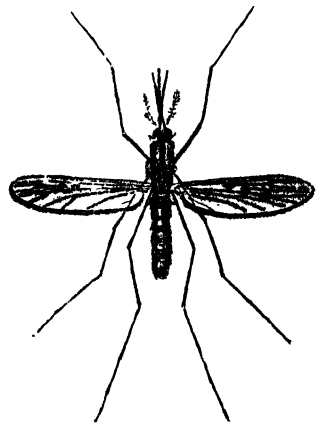


Fig. 392.—*Anopheles maculipennis*, female.¹

¹ A magnifying glass is necessary for identification from these drawings.

wider and taper acutely ; in *typicus* the scales are wider and taper less acutely than in *messeæ*, but more acutely than in *atroparvus* ; in *sacharovi* the scales are widest in the centre and taper gradually.

A. maculipennis typicus has not been found in England, but in Norway, the Black Forest and the Hartz Mountains ; *messeæ* in the fresh waters of Europe, its southerly range being Italy and the Balkans ; *melanoon* favours the rice-fields of North Italy and South-East Spain ; *atroparvus* is a salt-water breeder on the North Coasts of Europe ; *sacharovi* (*elutus*) replaces *atroparvus* in the south ; *labranchiæ* takes the place of *atroparvus* in North Italy and is the dominating variety in the Campagna. *Atroparvus* and *messeæ* are the only two varieties found in England.

The subdivisions of *A. maculipennis* are supported by biological differences in breeding-places, sexual behaviour, and habits. *Atroparvus* breeds in salt water : *messeæ* in fresh. *Atroparvus* does not go into complete hibernation.

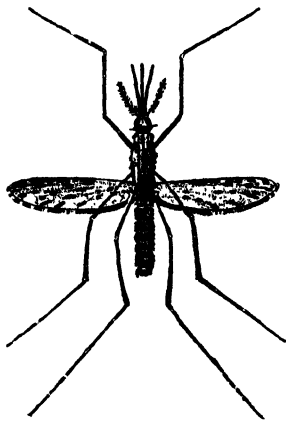


Fig. 393.—*Anopheles gambiæ*.¹
× 6

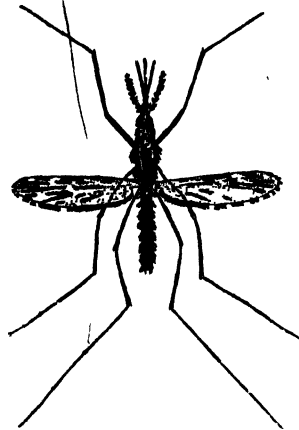


Fig. 394.—*Anopheles funestus*.¹
× 6

All varieties are equally susceptible to malarial infection, and although some prefer to feed on animals, there is never any insurmountable barrier. In almost the whole of northern Europe *A. maculipennis* lives on domestic animals, and man is protected from malaria by the deviation of anopheles by animals. In the malarious regions of southern Europe *maculipennis* bites man persistently. The principal reason for differences in behaviour in the north and south, is that the anopheles population of the latter region consists of varieties—*labranchiæ* and *sacharovi*—which feed upon man. The races *typicus* and *melanoon* are rarely associated with malaria. *Messeæ* is deviated by animals and goes completely into hibernation in winter. *A. occidentalis*, Dyer and Knab, is identical with *A. maculipennis*, and has the same biological varieties. It occurs along the northern borders of the United States, and in southern Canada, dipping in a southerly direction along the Pacific coast into Mexico, where it is now known as *A. maculipennis*, var. *freeborni*.

Sinton and Shute, in a report upon the longevity of mosquitoes in relation to the transmission of malaria in nature, obtained no evidence that, among healthy specimens of *A. maculipennis*, var. *atroparvus* infected with *Plasmodium*

¹A magnifying glass is necessary for identification from these drawings.

vivax and kept under conditions favourable to longevity, there is any noteworthy decrease in life as the result of the plasmodial infection.

Although available evidence adds little support to the suggestion that plasmodial infections may be a serious cause of mortality amongst anopheline mosquitoes in nature, especially *A. maculipennis*, var. *atroparvus*, it does not offer any satisfactory explanation of the reason why some anophelines are important as malaria-carriers under natural conditions, while others are not.

A. gambiae (*A. costalis*) (Fig. 393) is the most widespread and dangerous malaria-carrier in Africa. Recently it extended its range northwards into Upper Egypt. In 1930 it was introduced from Senegal into Natal (Brazil), spreading with great rapidity and concurrently with epidemic subtertian malaria, but it has now been exterminated (1942).¹ Malaria in Central Africa has a relatively high endemicity based on several factors, the chief being that *A. gambiae* has a high man-biting frequency. It is estimated that the chance of this mosquito

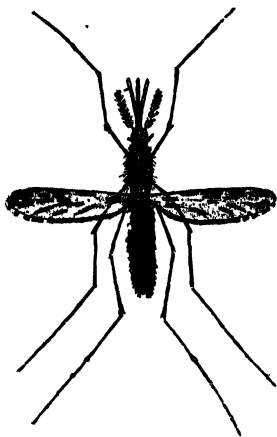


Fig. 395.—*Anopheles superpictus*.²
× 6

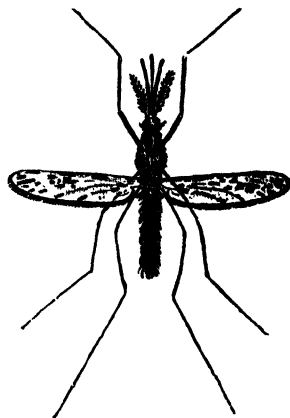


Fig. 396.—*Anopheles stephensi*.²
× 6

feeding on man during its lifetime is 136 times greater than that of *A. culicifacies* in Madras and it has a relatively high expectation of life of 13 days. It breeds in almost any collection of water, if fully exposed to the sun, such as wayside puddles, borrow pits, wells, flood-water, pools in river beds, slightly brackish or muddy, as well as clear water. In Somaliland during the dry season it aestivates in deep wells, thus accounting for its apparent absence. Normally it does not breed in rivers except when they are partially dried. It is domestic in habits, and bites man readily. Another allied species, *A. melas*, described by Thomson and established as a species by Ribbands, is a salt-water breeder (46 per cent. sea-water) and is co-extensive with the *Avicennia* mangrove. It is a melanistic coastal form extending from the Gambia to Nigeria. There is often an extra band on the palpi of the female. The egg differs in possessing an inner white rim; there is a difference also in the larval pecten. About 4 per cent. are naturally infected with malarial sporozoites.

Avicennia nitida mangrove is associated with a sea-grass and resembles an apple tree in appearance, growing in scattered, isolated "orchards" above

¹ International Health Division of the Rockefeller Foundation (Soper and Wilson), *Anopheles gambiae* in Brazil, 1943. The Rockefeller Foundation.

² A magnifying glass is necessary for identification from these drawings.

neaptide. Halcrow (1957) has described a new subspecies of *A. gambiæ* from Mauritius. It is a salt-water form. The adults possess four pale palpal bands. It is known as *A. gambiæ littoralis*.

A. funestus (Fig. 394) is the second most widespread and important malaria mosquito in Africa with the exception of the North. For breeding it needs shade in grassy-edged, sluggish streams with clean water; it never breeds in puddles without vegetation. The adult is domestic, bites man readily, and enters houses. It usually breeds in streams outside towns and is therefore a more rural species, being particularly dangerous in streams of foothills which are independent of local rainfall. The sporozoite rate may be 5 per cent. and endemic malaria is kept going by this species. In North Africa and in Egypt these two species are replaced by *A. multicolor* and the brownish-coloured *A. sergenti*, the former of which usually breeds in brackish water, the latter in fresh-water puddles. In the Delta region *A. pharænsis* plays a part in malaria transmission. In Israel and Syria *A. bifurcatus* breeds in wells and plays a definite rôle in endemic malaria during the winter season.

There are between 40 and 50 species of anopheles in Asia.

A. superpictus (Fig. 395) is often found in streams and in the shelter of rocks, especially in partially dried-up rivers in summer time. In Israel it hibernates in caves. Control is difficult.

A. stephensi (Fig. 396) is a town mosquito, the chief malaria-carrier in Bombay, but in Calcutta is almost a non-carrier, feeding mostly on cattle. It breeds chiefly in wells, and in closed cisterns, roof gutters and barrels, in close contact with man, who is readily infected. As with *A. maculipennis* there are subvarieties distinguished by their eggs. There are two main races, urban and rural. This is the most important single malaria vector in the Persian Gulf and, owing to its attacks, the disease is hyperendemic in the large Saudi-Arabian oases, especially near Dhahran and Al-Hasa oilfields which provide numerous breeding places. In the dry season it continues to breed at the bottom of deep wells.

A. subpictus and *A. vagus* are similar in appearances and habits. They are the commonest species in India and breed in many situations, in puddles, ponds and rice fields. Both are common in houses. They are mostly zoöphilic and therefore not of importance as malaria carriers. In Java *A. subpictus* carries malaria and breeds in brackish water.

A. culicifacies (Fig. 397), is the chief vector in India and Ceylon. This species, like *Culex*, assumes the horizontal stance. In malaria epidemics such as that of 1933-35, 20 per cent. are infected. This *Anopheles* breeds in sunlight, in clear water pools, especially dried-up rivers (as after drought in Ceylon), small irrigation channels and seepages from larger canals, wells and ornamental waters. It becomes abundant after excessive rain with high atmospheric temperatures. The transmission season therefore is generally brief, about six weeks. In Eastern India, especially in Bengal, this species is scarce. In some parts of India, though prevalent, it is not an important vector.

A. minimus (Fig. 398), *fluviatilis*, *varuna* and *aconitus* all breed in streams, and in habits and appearance resemble *A. funestus*. Larvæ are found mostly in natural streams, especially those edged with grass, and in irrigated rice fields. (Rice growing in lowland districts in natural swampland, when the water is muddy, is not dangerous, but the same fields in irrigated areas in the foothills of Assam, Northern India and the Philippines are especially malarious.) Thus, in Assam and Northern Bengal, especially in the tea gardens, *A. minimus* is almost the chief malaria-carrier, being a man-biter by preference and breeding in clear water in drains and streams. In the cold season, when the rivers are in spate, *A. minimus* retires to more suitable localities. *A. fluviatilis*, like the latter,

breeds in the Himalayan foothills down to Southern India, and is responsible for the malaria of the foothills in the tea and coffee estates in Southern India. *A. varuna* is capricious also in relationship to malaria; it breeds in tanks and reservoirs in Bengal, but is not important in Southern India. It is common in Ceylon, but is not a vector there, but is an important species in Java and Philippines. *A. aconitus* is not important in India.

All these are absent when the foothills are in a virgin state. Malaria there is really man-made, due to clearing of trees and undergrowth. Control means reversion to shade by planting shade bushes over streams. *A. leucosphyrus* (*balabacensis*) is found in India to Celebes, Java to Formosa; its variety *hackeri* occurs in Malaya. It is an elusive jungle-breeding mosquito and an important vector in Borneo, Sumatra, Celebes, Indo-China and Burma (McArthur, 1951).

A. hyrcanus and *A. barbirostris* are similar in appearance and habits. They commonly breed together in swamps or cultivated rice fields, but readily take

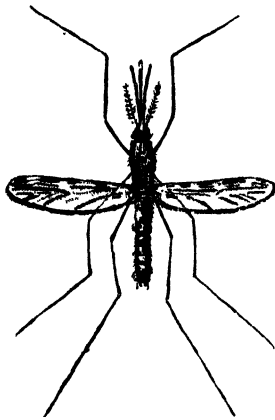


Fig. 397.—*Anopheles culicifacies*.¹
× 6

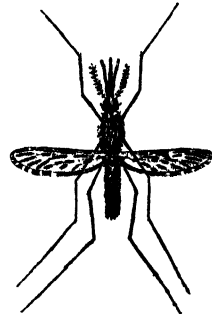


Fig. 398.—*Anopheles minimus*.¹
× 6

to feeding on cattle, and on this account are usually of no importance in India and China, but in the latter country, as well as in Java, they are important in cattle-free areas.

A. maculatus (Fig. 399) is the chief efficient carrier of malaria in Java and in the rubber-growing districts of Malaya. It does not occur in the natural jungle, unless this is cleared, but is found in streams, seepages, hoof-marks, etc., and is a man-biter. Shading and covering streams and drains have been effective in prevention. *A. maculatus* is also common in the foothills of Assam and Ceylon, but is zoöphilic there and consequently not so important.

In dense natural Malayan jungle mosquitoes do not breed, but when it is cleared, *A. umbrosus* appears and probably carries malaria. This species favours shade; when this is completely abolished it disappears. *A. sundaicus* (*ludlowi*) (Fig. 400) breeds freely in Java in salt-water fish ponds, and in cleared mangrove swamps, where the pools are filled with brackish water. Important vectors in Bengal (Iyengar) are: *A. philippinensis* (in the plains), *A. sundaicus* (in the delta), and *A. minimus* (submontane area).

In North America there are only nine species of anopheles, of which three are regarded as important malaria carriers:

A. maculipennis, var. *freeborni*, invades houses freely.

¹ A magnifying glass is necessary for identification from these drawings.

A. punctipennis is the most widespread anopheline; it has black and yellow scales on its wings, and breeds in cool shaded pools, seldom entering houses.

A. quadrimaculatus ranges from Mexico to Canada and is the chief vector of malaria in Eastern, Central and Southern United States. The wings have four distinct spots. It breeds in still clean water, and requires sunshine.

A. pseudopunctipennis is widespread from the Argentine through Central America. It breeds in sunlit pools along the courses of receding streams, the larvæ feeding on green algæ. It rarely enters dwellings. This species (like *A. maculipennis*) can be divided into at least two subvarieties according to the colour and pattern of the eggs.

A. albimanus (Fig. 401) is the most important anopheline in the Caribbean. Whilst preferring sunlit open pools, it develops also in brackish or salt water. In South America, in addition to the species mentioned, there is another important species: *A. tarsimaculatus*. *A. darlingi* has recently been recognized as

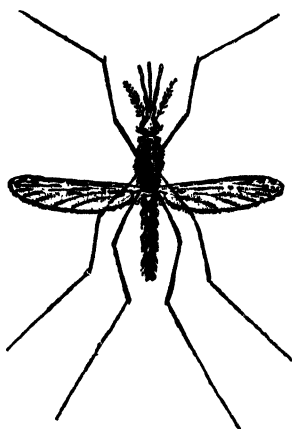


Fig. 399.—*Anopheles maculatus*.¹
× 6

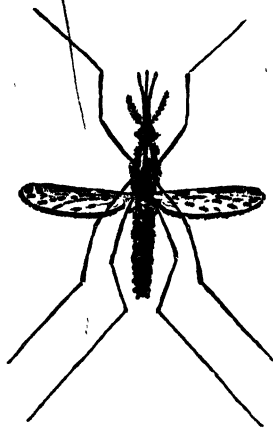


Fig. 400.—*Anopheles sudaicus*.
× 6

important carrier in British Guiana, British Honduras, Brazil and Venezuela. The adults enter houses and bite man greedily. The larvæ are found in collections of water rich in vegetation. *A. aquasalis*, an important carrier, in coastal regions breeds in salt water. *A. bellator* is the most important species in Trinidad, where it breeds in the water which collects in epiphytic plants or bromeliads. Its extermination is very difficult.

A. bellator is one of four species of the subgenus *Kerteszia*. They all breed in water collections amongst the leaves of bromeliads. The principal host plants of these epiphytes are *Gravisia aquilegia*, *Hohenbergia stellata*, and *Wittmachia lingulata*. Some "immortelles" (*Erythrina*) harbour a hundred or more of these parasites, and they are grown as wind screens to protect the cacao. Under this cover *A. bellator* is active throughout the day and bites readily at noon. With one exception 1,600 species of bromeliads occur in the New World. Some grow on the ground: others attack bare trees at different heights and they may even attach themselves to telegraph wires. The so-called tank, formed by overlapping leaves in broad-leaved species, holds over a gallon of water and it is in these that *Kerteszia* breed. In Trinidad the mosquito-breeding bromeliads

¹ A magnifying glass is necessary for identification from these drawings.

grow upon quick-growing shady trees planted between cacao bush. They can best be controlled by copper sulphate spraying. Mango trees are encouraged as their dense foliage is unfavourable to bromeliads.

In Australia, Melanesia, and Polynesia only one species of *Anopheles* is the vector of malaria, *A. punctulatus* (Fig. 402) which breeds in stagnant swamps with abundance of algæ, in temporary rain pools, roadside puddles, and even in beached native canoes; it is also found in paddy fields and shady forest pools. It has an unusually wide range of flight, and seeks human blood in preference to that of birds or animals. There are several forms of *A. punctulatus*, such as *A. punctulatus punctulatus* and *A. p. farauti*. All have much in common, though behaviour may differ according to local conditions. Thus *A. p. farauti* has no preference for either human or animal blood; in *A. p. punctulatus* anthropophilism is marked. All are more attracted to indigenous peoples than to the white man.

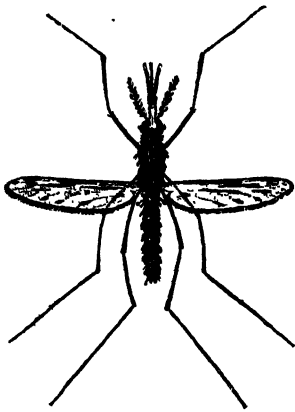


Fig. 401.—*Anopheles albimanus*.¹
× 6

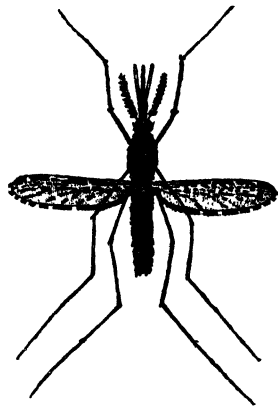


Fig. 402.—*Anopheles punctulatus*.¹
× 6

LIST OF ANOPHELES VECTORS OF MALARIA REGIONS AND TYPICAL BREEDING PLACES

(Those marked with an asterisk are the most important vectors)

EUROPE.

<i>A. algeriensis</i> .	W. Mediterranean.	Marshes, sluggish streams.
<i>A. claviger</i> (<i>bifurcatus</i>). (Fig. 358)	S. Europe, Cyprus, Greece, Italy.	Wells, larvæ hibernate in cisterns.
<i>A. hyrcanus</i> (<i>Crawfordi</i>).	Macedonia and E. Medi- terranean.	Marshes.
<i>A. maculipennis</i> (<i>typicus</i>). (Fig. 359)	Rumania, Hungary, E. Czechoslovakia, S. Yugoslavia, Russia. (Not in England.)	Fresh water, including hill regions.

A magnifying glass is necessary for identification from these drawings.

- **A. maculipennis atroparvus*. N. Holland, Germany, Portugal, W. Spain. Brackish water, marshes, lagoons.
- **A. maculipennis labranchiae*. Dalmatian coast, Italy, S.E. Spain, Sicily, Sardinia, Corsica. Brackish water, marshes, lagoons, fresh water in rice fields.
- A. maculipennis messeae*. Hungary, Lower Danube, C. Russia. Alluvial drainage.
- A. plumbeus*. Russia, N. Europe, England. Tree holes, forest species.
- A. sacharovi (elutus)*. S.E. Europe, Russia (Caspian). Brackish water, stagnant pools, puddles, sluggish streams.
- A. superpictus*. (Fig. 395) E. Mediterranean, Spain, Italy, S. Russia, Algeria, S. India, Persian Gulf, Afghanistan, Baluchistan. Pools, drains, backwaters, river beds, edges of flowing water.

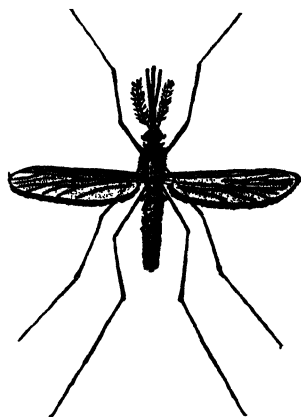


Fig. 403.—*Anopheles bifurcatus*.¹
× 6

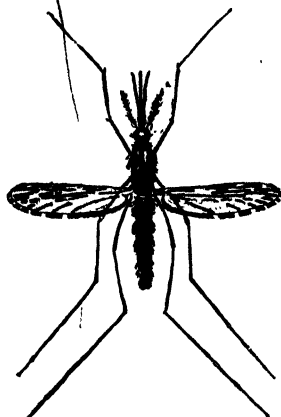


Fig. 404.—*Anopheles annularis*.
(Syn. *fuliginosus*) × 6

ASIA.

- A. aconitus*. Indonesia, Malaya. Irrigation channels, swamps, ponds, rice fields.
- A. annularis (fuliginosus)*. Indonesia, Ceylon, Burma, Thailand, Indo-China. Swamps, pools, rice fields.
- (Fig. 404)
- A. balabacensis* (see *A. leucosphyrus*).
- A. barbirostris*. Indonesia, India, Ceylon, Burma, Thailand, Indo-China, Borneo, Celebes, Philippines. Swamps, pools, ditches, rice fields.
- (Minor importance)
- A. claviger (bifurcatus)*. Urban vector, Syria and Palestine. Wells and cisterns.
- (Fig. 403)
- A. culicifacies*. (Fig. 397) S. Arabia, India, Ceylon, Burma, Thailand, S. China. Clear, running slow streams, irrigation channels, wells, borrow pits.
- A. fluviatilis (listoni)*. India, Ceylon, Thailand, Indo-China, Turkestan. Streams and pools.
- **A. hyrcanus*. Java, Celebes, Malaya, China. Pools in rice fields.

¹ A magnifying glass is necessary for identification from these drawings.

**A. hyrcanus* complex comprises 7 forms which, regarded as distinct species, have been named. On the whole they are swamp breeders with preference for animal blood. Individual species show differences in their biology. Some prefer sunlit waters; others shady pools, as follows:—

A. hyrcanus crawfordi.

A. h. sinensis. (Fig. 406.)

Important vector in
China and Japan.

A. h. nigerrimus.

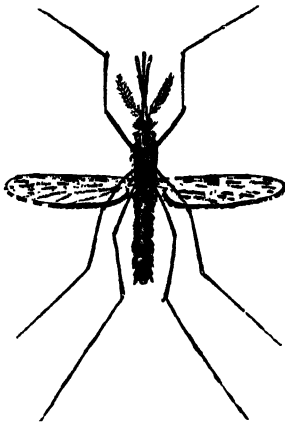


Fig. 405.—*Anopheles multicolor*.¹
× 6

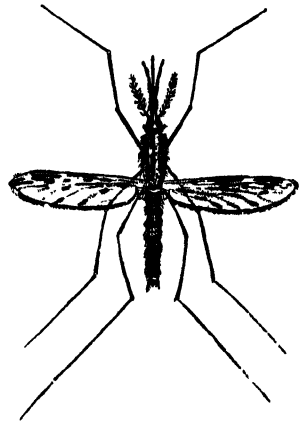


Fig. 406.—*Anopheles hyrcanus sinensis*.¹ × 6

A. h. lesteri.

A. h. indiensis.

A. h. argyropus.

A. h. pediceniatus.

A. jeyporiensis.

S. China, Indo-China,
Assam, E. India.

Rice irrigation channels and
streams.

**A. jeyporiensis candidiensis*.
(Important vector S.W.
China, Tonking)

India, Malaya, China.

Running water and ditches.

A. kochi.

Indonesia, Malaya, Assam.

Fresh-water ponds, grassy
edges of mountain
streams.

A. leucosphyrus.

Borneo, Labuan, Dutch
E. Indies, Java to
Formosa.

Jungle-breeding mosquito,
Dirty jungle pools,
springs, hoofprints.

This mosquito is now regarded as a complex of six members scattered through Asia. The Borneo representative is *A. l. balabacensis*.

¹ A magnifying glass is necessary for identification from these drawings.

<i>A. maculatus</i> . (Fig. 399)	Philippine Islands, Borneo, Indonesia, India, Ceylon, Indo-China, Formosa, S. China, Thailand.	Seepage areas in sunlight or open hill streams.
<i>A. maculipennis (typicus)</i> .	Asiatic Russia.	Fresh water, including hills.
* <i>A. maculipennis atroparvus</i> .	Mongolia.	Brackish water in coastal areas.
<i>A. maculipennis messeæ</i> .	Asiatic Russia.	Fresh water, including hills.
<i>A. mangyanus</i> .	Philippines.	Clear flowing streams in mountains and forests.
* <i>A. minimus</i> . (Fig. 398)	E. India, Ceylon, Burma, Assam, Indo-China, S. China, Formosa.	Grassy springs, streams, ponds, ditches, rice fields.
<i>A. minimus varuna</i> .	India, Ceylon.	ools, ditches, wells.
<i>A. multicolor (turkhudi)</i> . (Fig. 405)	Persia, India.	pools, irrigation channels and brackish water.
<i>A. novumbrosus</i> .	Malaya.	Shade breeder, jungle-covered swamps.
<i>A. letifer</i> (formerly <i>umbrosus</i>).	Malaya, Indonesia, Assam.	stal hills and plains.
<i>A. pattoni</i> .	N. China.	Slow mountain streams, rice fields.
<i>A. philippinensis</i> .	W. India, Bengal, Assam, Burma, Malaya.	Rice fields, lakes, small bodies of water.
* <i>A. stephensi</i> . (Fig. 396)	S. India, Iraq, Ceylon, Arabia.	Pools and wells, cisterns adapted to towns.
<i>A. subpictus (rossi)</i> .	India, Formosa, S. China, Assam, Indonesia, New Guinea.	Polluted pools, often brackish.
* <i>A. sundaicus (ludlowi)</i> . (Fig. 352)	E. India, Burma, Andamans, Malaya, Indonesia, Borneo.	Usually brackish pools.
* <i>A. superpictus</i> . (Fig. 395)	Asia Minor to India (Punjab).	Pools, drains, backwaters.
<i>A. tessellatus</i> .	Formosa, S. China, Indo-China, Thailand, Malaya, Assam, Maldives.	Shaded pools, puddles, brackish swamps.
<i>A. multicolor (turkhudi)</i> .	Mediterranean, Ethiopia, India.	Rain pools with algæ.
<i>A. umbrosus</i> .	Philippines, Borneo, Labuan, Indonesia, Celebes.	Peaty marshes in virgin jungle (sometimes brackish).
<i>A. vagus</i> . (Minor importance)	India, Andaman Islands, E. Indies, S. China, Formosa.	Small collections of muddy water, ponds and rice fields, also in brackish water.

AFRICA.

<i>A. algeriensis</i> .	N. Africa (W. Mediterranean).	Marshes, sluggish streams.
<i>A. brunniipes</i> .	Leopoldville, Belgian Congo.	
* <i>A. funestus</i> . (Fig. 394)	W., S., Central and E. Africa, Congo.	Grassy pools and streams

- **A. gambiæ*. (Fig. 393) *Ibid.*, also Upper Egypt and Sudan, Arabia, Madagascar, Mauritius. Usually muddy pools without vegetation, but exposed to sunshine. Occasionally brackish water.
- A. hancocki*. Sierra Leone, Liberia, Cameroons, Uganda, Belgian Congo. Clear water in grassy water-holes, in ditches, wells and swamps.
- **A. hargreavesi*. W. Africa and Belgian Congo. Sides of streams, swamps (vegetation).
- A. maculipalpis*. French Cameroons.
- **A. maculipennis labranchiæ*. N. Africa (W. Mediterranean). Brackish pools, marshes, lagoons, rice fields (warmer water than for *atroparvus*).
- **A. melas*. Gambia, Sierra Leone, Nigeria, W. Africa, Mauritius. Brackish and salt water in mangrove swamps.
- A. moucheti*. C. and E. Belgian Congo, Uganda. Stream banks, pools (vegetation) and big rivers.
- A. moucheti nigeriensis*. C. Africa, Ethiopia. Clear water with *Pistia* and other vegetation.
- A. multicolor*. (Fig. 405) N. Africa deserts, Egypt. Pools, irrigation channels, brackish and salt water.
- A. nili*. Tropical Africa, Liberia. Clear, shaded flowing water.
- A. pharænsis*. Egypt, Tropical Africa, Madagascar. Flooded grasslands, swamps.
- A. pretoriensis*. Transvaal. Pools and streams.
- A. rufipes*. Sudan and French Guinea. Sunny pools.
- **A. sacharovi (elutus)*. E. Mediterranean. Brackish pools, puddles.
- A. sergenti*. N. Africa, Nile Delta. Pools, drains, hoofprints.
- **A. superpictus*. (Fig. 395) N. E. Africa. Pools, drains, backwaters, river beds, edges of flowing water.

AMERICA.

- **A. albimanus*. (Fig. 401) Coastal Mexico, C. America, W. Indies. Swamps, marshes, streams.
- A. (Nyssorhynchus) albitarsis*. Argentina, Brazil, Guianas, Paraguay, Venezuela. Large ponds, marshes, overflow areas.
- **A. (Nyssorhynchus) aquasalis (tarsimaculatus, in parte)*. (Easily deflected to animals) Nicaragua, Br. Guiana, Panama, Trinidad, Brazil. Nectar feeding by both sexes. Shaded, or sunlit, brackish tidal swamps and fresh water rice fields.
- A. argyritarsis*. Brazil, Colombo, Guianas, Venezuela. Pools, ditches, seepage.
- **A. (Kerteszia) bellator* and *A. (Kerteszia) cruzi* Trinidad, Venezuela, Brazil, "Forest Species," "Domestic Species." Exclusively in collections of water at base of bromeliads, epiphytic on shade trees, such as "immortelle" (*Erythrina*). Bite man preferably. Enter houses. Active in day-time in deep shade.
- A. crucians*. S. and E. U.S. Coastal, Mexico. Brackish and fresh water.

* <i>A. (Nyssorhynchus) darlingi</i> .	Bolivia, Brazil, Colombia, Peru, Venezuela, Argentina. British and Dutch Guiana.	Ground pools, side pools of rivers, with vegetation, muddy road pools.
<i>A. gambiæ</i> , introduced 1930 into Brazil from Senegal (now exterminated 1942 ¹)	Brazil (Rio Grande, Ceará).	Grassy pools, streams, brackish water.
* <i>A. maculipennis freeborni</i> .	Pacific slopes of U.S. and New Mexico.	Clear fresh seepage (sometimes brackish), overflow, rice fields.
<i>A. maculipennis aztecus</i> .	Central Mexico.	Clear and dirty water.
<i>A. oswaldoi noræstensis</i> .	N. and S. Brazil.	Shaded fresh water in jungle.
<i>A. punctimaculata (malefactor)</i> .	Central America (Panama, Salvador), Colombia, Trinidad, S. America.	Shaded ground pools with leaves, swamps, sluggish water. Bites man. Houses entered at night. Jungle mosquito.
<i>A. pseudopunctipennis</i> .	Argentina (N. W.), Chile, Peru.	Stream beds with algæ.
* <i>A. quadrimaculatus</i> .	S. and E. U.S.A., N. E. Mexico.	Pools, ponds, lakes, lagoons, swamps.
<i>A. walkeri</i> . (Doubtful importance)	N. U.S.A.	All kinds of pools.
AUSTRALIA AND PACIFIC.		
<i>A. amictus hilli</i> .	N. Queensland, New Guinea.	Pools and marshes.
<i>A. annulipes</i> .	New Guinea, Australia, New Hebrides.	Pools, marshes, creeks, occasionally brackish water.
<i>A. bancrofti</i> .	New Guinea.	Shallow, slow - running water with vegetation.
* <i>A. punctulatus</i> . (Fig. 402)	Moluccas, New Guinea, New Britain, Solomons.	Pools, swamps, puddles. Usually fresh.
* <i>A. punctulatus farauti (moluccensis)</i> . (Most important vector)	New Hebrides, Solomon Is., N. Australia, New Guinea, Moluccas, Bismarck, Archipelago.	All kinds of water, brackish and salt, clear or standing.
* <i>A. sundaicus (ludlowi)</i> . (Fig. 400)	Moluccas.	Usually brackish pools.

TRIBE CULICINI

This large tribe contains over 500 species and some 20 genera. The scutellum is trilobed, each lobe bearing bristles. The abdomen is blunt and completely clothed with broad flat scales. The eighth segment of the larva is drawn out into a respiratory siphon with a well-developed pecten and four gills provided with tufts of hairs situated on a projection anterior to the respiratory siphon. Culicines living in water with little chloride have large anal gills. There are no rosettes or palmate hairs as in anopheles. The pupæ are similar to those of anopheles, but the respiratory trumpets are longer.

The following are the main characteristics of culicines in contradistinction to those of anophelines :

¹ This feat provided the best example of species eradication. Spraying with pyrethrum (*Flit*) to kill off adults, and Paris Green for larvae, were the chief methods employed.

(1) The eggs are not provided with air floats, either laid separately or stacked in rafts (Fig. 407).

(2) The larva breathes through a pair of spiracles, situated at the tip of a tail-like tube or siphon, projecting dorsally from the 8th abdominal segment. It hangs head downwards from the water-surface, supported by the capillary action of five hinged valves surrounding the tip of the siphon. It sweeps for floating, as well as suspended, particles of food with *mouth-brushes* below surface level, or else dives to the bottom (Fig. 408).

(3) The pupa has cylindrical respiratory trumpets and usually a branched hair at each "apical" corner of 3-7 abdominal segments. It has no accessory hair on the ventral surface of the paddle.



Fig. 407.—*Culex fatigans* egg-raft. (After Sambon.)

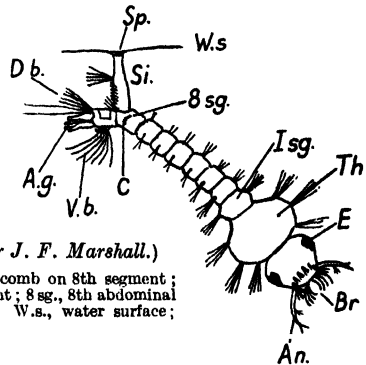


Fig. 408.—Larva of *Culex fatigans*. (After J. F. Marshall.)

A.g., anal gills; An., antenna; Br., mouth brush; C, comb on 8th segment; D.b., dorsal brush; E, eye; I sg., 1st abdominal segment; 8 sg., 8th abdominal segment; Si., siphon; Sp., spiracle; Th., thorax; W.s., water surface; V.b., ventral brush.

(4) The adult has an abdomen densely covered with scales. The female has short and slender palps, from one-fifth to one-half as long as the proboscis. The male has, as a rule, long hairy palps which have a "plume-like" appearance. This mosquito usually rests with proboscis and abdomen forming an obtuse angle, the abdomen being more or less parallel with the supporting surface (Fig. 409).

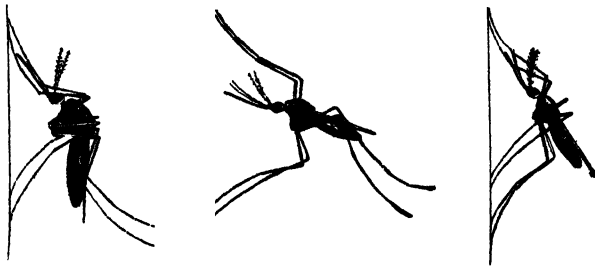


Fig. 409.—Resting position of *Culex fatigans*, *Anopheles hyrcanus*, and *Anopheles maculipennis*.

Genus: *Culex*.

The following are forms of the *Culex pipiens* complex: *Culex pipiens pipiens*, *C. pipiens fatigans*, and *C. pipiens form molestus*.

Culex fatigans (Wiedemann, 1828) (Fig. 410) is a nocturnal species, found in the tropics and subtropics, common in houses; it breeds in water tubs or any collection of water and can be distinguished from anopheles by the position assumed on resting (Fig. 409). The palpi are shorter than the proboscis in the female. This species was first established by Manson (1878) as the intermediary of *Wuchereria bancrofti*. It also transmits *Dirofilaria immitis* of the dog and various plasmodia of birds.

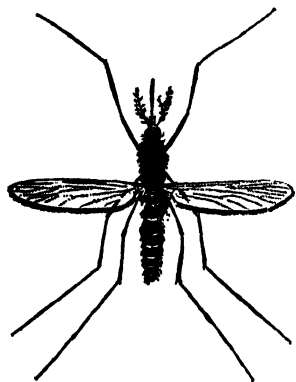


Fig. 410.—*Culex fatigans*. $\times 4$.

C. pipiens (Linn) is the common house mosquito of East and North America and the Pacific coast, ranging through Europe, China and portions of South America. It is brownish-grey and the basal white bands on the abdomen form lateral basal triangular patches. It lays eggs, by preference, in polluted water. It bites viciously and the hum produced is high pitched. It transmits *W. bancrofti* in Egypt, China, S. America, Queensland and Melanesia, also the virus of human and equine encephalomyelitis. Differs mainly from *C. fatigans* by the character of the male genitalia. According to Marshall there are two species, one, the man-biter, is *molestus*; the term *pipiens* being retained for zoophilic form, which feeds mostly on birds.

GENUS MANSONIA (TÆNIORHYNCHUS) (Edwards)

SUBGENUS MANSONIOIDES (Fig. 411)

This genus occurs in tropical and Central America, tropical Africa, and in Asia, especially Malaya, but is less important in temperate North America, Europe, and Australia. These mosquitoes are recognizable by the very broad asymmetrical wing scales, which are of two colours, white and grey, like salt and pepper, but which do not make conspicuous pale and dark areas. The palpi of the male are longer than the proboscis; the penultimate segment is turned upwards, while the last segment is minute, and is turned downwards. The end of the abdomen of the female curves upwards, so that only six and a half segments are visible dorsally. The eighth segment is entirely retracted, is of a peculiar form, and carries a row of strongly chitinized teeth on the tergite. The arrangement of these teeth and the shape of the lobes of the sternite are of value in identification. There are five species of importance which are concerned with the transmission of *Brugia malayi*: *M. annulatus*, Leic., *M. annulifera* (Theo), *M. indiana*, Edwards, *M. longipalpis*, v. d. Wulp,

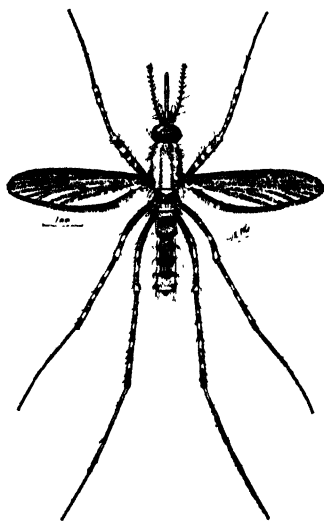


Fig. 411.—*Mansonioides annulifera* (Theo.) ♀ (McKay.)

and *M. uniformis* (Theo). The members of this subgenus are of little or no importance as vectors of *W. bancrofti* (Mattingly, P. F., 1951).

The larvæ of mansonioides are readily recognizable by the peculiar form of the respiratory siphon, which is adapted for piercing plant tissues (Fig. 412).

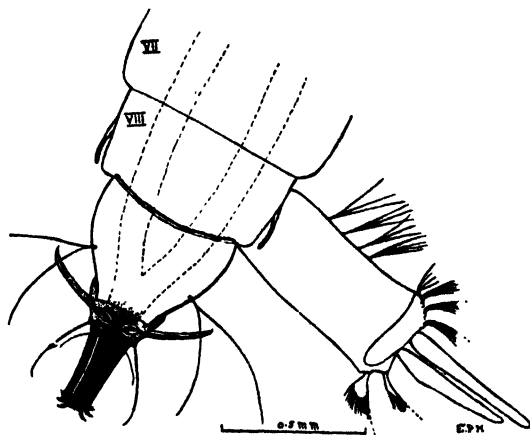


Fig. 412.—Respiratory siphon and terminal segments of larva (dorsal view) of *Mansonioides*.

(From *Bulletins from Inst. for Medical Research, Federated Malay States; Endemic Filariasis in the F.M.S.* (Poynton and Hodgkin).)

This structure is short, and has a conical base and a distinctive black tip made up of several parts, one of which has a saw edge and ends in a ring of retractable hooks. The known larvæ closely resemble one another. The pupæ are also distinguishable by the form of the respiratory horns which, like the siphon of the larvæ, are modified for piercing plant tissues (Fig. 413). Each horn is long and terminates in a narrow, strongly chitinized portion, which bears a pair of

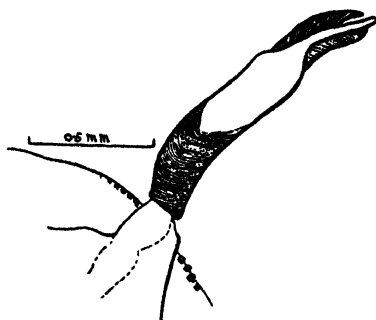


Fig. 413.—Respiratory horn of pupa of *Mansonioides*.

feather-like structures and ends in a sharp point. All species of mansonia are man-hunters and fierce biters, and attack either in or out of doors. Primarily night-biters, in the jungle they feed at any time. The eggs are laid in small batches, containing a hundred or more, on the underside of leaves of water

plants just above the surface of the water. The most characteristic peculiarity, and the one which defines the distribution of the genus, is the habit of the pupæ and larvæ of obtaining air from the submerged portions of water plants.

The larva of *mansonioides* inserts its respiratory siphon into the air-containing tissues, and remains there until forcibly removed. The pupæ do likewise. The roots appear to be the part of the plant most favoured. Different species have a preference for certain water plants, and the type of water in which they prefer to grow. *M. annulifera*, *M. indiana*, and *M. uniformis* are most easily found among the roots of water plants floating and growing in exposed situations, especially *Pistia stratiotes*, a plant which floats with hanging roots in still water. *M. uniformis* has a preference for the water hyacinth (*Eichornia crassipes*) and swamp grass (*Isachne australis*). The food of the larvæ consists of fine particles of organic matter which are freed from coconut husks in the process of coil and rope-making.

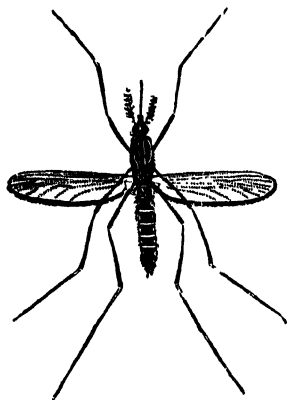


Fig. 414.—*Aedes aegypti*.¹
female. × 4.

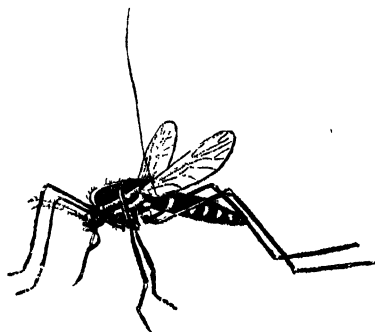


Fig. 415.—*Aedes scutellaris pseudo-scutellaris*.¹ Side view, showing buckling of proboscis sheath in the act of biting.
× 4.

GENUS *ÆDES* (Meigen, 1818), Subgenus, *Stegomyia*

This genus is widely distributed. These are mostly black and white insects with white, silvery yellow bands or spots on the thorax and legs, for which reason they are generally known as "tiger mosquitoes." Certain species (*A. aegypti* and *A. albopictus*) are frequently found in ships.

*Aedes aegypti*² (Fig. 414). Syn.—*A. argenteus*, *Stegomyia fasciata*

This occurs all over the tropics and subtropics, 40° North and South of Equator, and in Europe at the level of Gibraltar. It is a domestic species rarely breeding more than 100 yards from houses, and can be recognized by the peculiar lyre-shaped design—two dull-yellow parallel lines in the middle and a curved silvery line on each side of the thorax. The proboscis is not banded, but the abdomen is banded basally. The last hind tarsal joint is all white and some of the other tarsal joints are marked basally by light bands. It bites avidly, mostly by night. The eggs are laid in small dark receptacles, e.g., water in tree-rot holes, tins, pots, coconut shells, cut bamboo, sagging eaves, plants, tops of pineapples, sisal leaves, vases in cemeteries, bilges of ships, old beer bottles, and car tyres. When deposited they are white, but darken in a few hours. If kept moist, the

¹ A magnifying glass is necessary for identification from these drawings.

² Mattingly (1957) has suggested that *argenteus* is correct.

*The reader is referred to the authoritative work by Sir S. R. Christophers (1960), Cambridge University Press.

larvæ develop in 12-24 hours ; they can resist drying for as long as six months. The larvæ then emerge when they are moistened.

Mattingly (1951) classifies the *A. ægypti* complex as:

A. ægypti type form, except inland in Africa, south of the Sahara.

A. ægypti ssp. *formosus*, Africa south of Sahara.

A. ægypti var. *queenslandensis*, a pale form. North Australia and coastal regions of Africa.

A. ægypti transmits the virus of yellow fever and dengue (p. 357). Although so widely distributed it does not occur abundantly in Australia, Malay States, China, Africa, and West Indies, where it is replaced by allied species. Under experimental conditions other species may transmit yellow fever, such as *A. vittatus* (*sugens*), *A. apicoannulatus*, *A. africanus*, *A. simpsoni* and *Eretmopolites chrysogaster*. Abundant throughout S. America and the S. United States, it does not occur in California. *A. leucocelænus* transmits jungle yellow fever in S. America.

A. leucocelænus represents a complex species, one extending from Costa Rica along the E. coast of America to Argentina. This divides into two subspecies at the extreme end of its range. *A. leucocelænus clarki* is found in Panama and Costa Rica.

In the control of aedes constant attention must be paid to minute details. Legal enactments should be passed for inspection of houses, compounds and buildings. Gutters should be prohibited, and tree-rot holes filled with sand and tar. In most tropical countries old tins are rolled out by rollers operated by the sanitary authorities.

A. vittatus (*sugens*), with six white spots on the thorax, usually breeds in rock-pools throughout tropical Africa. In Freetown, Sierra Leone, it is usually wild, but readily becomes domestic, and it may act as a vector of yellow fever in West Africa.

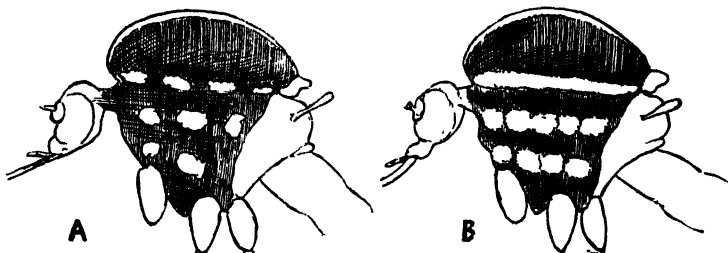


Fig. 416.—Diagrammatic representations of marking on thorax of (A) *Aedes albopictus* and (B) *Aedes scutellaris pseudoscutellaris*—lateral views.

A. albopictus (Skuse, 1895) (Fig. 416, A) is a commonly distributed species in the East, where it breeds in bamboos near dwellings. In general its habits resemble those of *A. ægypti*, but it is distinguished by the single broad median stripe in the scutum. It is a transmitter of dengue in Japan (see p. 359).

Members of the *A. scutellaris* complex are found throughout Indonesia and the Pacific. *Aedes scutellaris pseudoscutellaris* is found solely in Fiji (formerly known as *Stegomyia pseudoscutellaris* or *A. variegatus*) (Fig. 415). A new species, *A. s. polynesiensis*, has been separated by Marks (1951). It is found in Fiji as well as in Samoa, Ellice, Cook, Society, Austral, Tuamotu and Marquesas Islands.

A. s. polynesiensis closely resembles *pseudoscutellaris*. There are some small differences in the scales on the scutum, but the main distinction lies in the genitalia

of the male. In *polynesiensis* the basal lobe of the coxite is simple with setæ extending nearly to base dorsally, but without stout specialized setæ. There are also some minor distinctions in the papillæ of the tail of the larvæ. A third species, *A. (F.) fijiensis*, which breeds in the stems of the Taro (*Colocasia*) has also been found to be a hospitable host.

Polynesiensis is therefore the chief vector of the non-periodic Pacific filaria, *Wuchereria bancrofti* var. *pacifica*. Members of this group have also been proved to be the vectors of dengue in the Pacific. These two species (*pseudoscutellaris* and *polynesiensis*) are diurnal in habit, bite man, but may also feed on birds, pigs, horses, fowls and dogs. Their biting activity is in the afternoon (3-6 p.m.) with a low peak in the morning (6-8 a.m.). They do not rest in houses, but in the bush. The dispersal is limited, not exceeding 100 yards in 2-3 weeks. The distinguishing marks are three parallel white stripes on the mesothorax, and the incomplete white abdominal cross bands (Fig. 416, p). The larvæ resemble those of *A. ægypti*, but are distinguished by the lateral barbs of the comb scales, which are distinctly smaller and more delicate. The breeding places are peculiar; though readily entering houses, they are not domestic mosquitoes. They breed

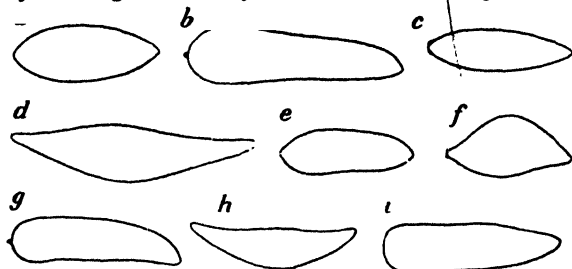


Fig. 417.—Various forms of mosquito eggs.

a, *Grabhamia dorsalis*; b, *Culex pipiens*; c, *Culex scapularis*; d, *Mansonia titillans*; e, *Aedes ægypti*; f, *Taniorhynchus fulvus*; g, *Culex fatigans*; h, *Janthinosoma lutzii*; i, *Taniorhynchus fasciolatus*.

mostly in small collections of water containing decaying vegetable matter, in the shells of coconuts, in crevices and holes in trees, in the artificial reservoirs in coconut trees used by Polynesians, in holes in coca-pods gnawed out by Pacific rats; in crab-holes, in bottles and tins lying about in the bush. The eggs, larvæ and pupa can withstand considerable desiccation.

Eighteen subspecies are now recognized such as *A. scutellaris tongæ*, *marshallensis*, etc., by Marks.

In campaigns against these mosquitoes, the introduction of predatory megarrhine larvæ has been attended in the Pacific by a considerable degree of success. Unless rotten wood is completely excavated, filling in tree holes by a mixture of sand and tar is unsatisfactory. A third species of the *scutellaris* group is found in Fiji, *A. s. horrescens*, the larvæ of which are clothed in hairs.

A. upolensis from Opolu Island, W. Samoa, is a new species described by Marks. It can be distinguished by the absence of a distinct patch of white scales on the lateral thorax, the lateral white markings do not extend to the bases of tergites IV-VIII as in related species and there are differences in the structure of the basal lobe of the male corite. It is a rain-forest species.

These species are extremely intolerant of sun and wind. Their main haunt is still, shady bush around native villages. Much has been done in the Gilbert and Ellice Islands by the removal of undergrowth, creating a thorough draught to the trade winds, which render their haunts untenable. Similar measures are being undertaken on a large scale in Fiji by native trained teams.

Genus: *Hæmagogus*.

This genus of mosquitoes is closely related to *Aedes*. It occurs in S. America, the adults are metallic blue and green due to their covering of scales on thorax and abdomen. Three species are vectors of sylvan (jungle) yellow fever: *Hæmagogus spegazzinii*, *H. spegazzinii falco*, and *H. capricorni*. They are separable only on the characters of the male genitalia and not at all as larvæ and pupæ. The larvæ of the group are "hairy" and are thus distinguishable from other species of *Hæmagogus* which are not vectors. They have been reared from captured females.

TRIBE: SABETHINI

Genus: *Sabethoides*.

These are jungle mosquitoes, suspected of transmitting jungle yellow fever in Brazil. In all three stages of their existence they are so characteristic that they have been distinguished as a separate tribe. The adults have a metallic lustre. The scales of all parts of the body are flat. There is a pair of very large procumbent bristles projecting from the crown of the head. The antennæ are similar in both sexes; the palpi short in the female and usually also in the male. The larvæ are generally predaceous and live in the water which collects in the axils and bracts of leaves, or is secreted by pitchers or other modified parts of plants. They are usually rather hairy and have smooth or stumpy antennæ. A siphon is present and there is a single row of scales on the sides of the eighth abdominal segment. The pupæ are characterized by the conspicuous fan of bristles at the postero-lateral angles of the eighth and ninth abdominal segments and by the small tail-fins. The most widespread species is *Trichoprosopon frontosus* which is widespread in S. America and transmits yellow fever by its bite under laboratory conditions.

FAMILY CERATOPOGONIDÆ (midges, gnats)

These are very small (1-3 mm. in length), slender, bloodsucking gnats, generally known as midges. In biting habits they resemble Simuliidæ and are frequently mistaken for them. The antennæ are plumose in the male, pilose in the female.



Fig. 418.—*Culicoides grahami* ♀ × 50.
(After Byam and Archibald.)

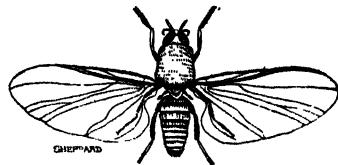


Fig. 419.—*Simulium damnosum*. × 10.

Amongst twenty or more genera comprising the family, the most important from the medical aspect are *Culicoides* (Fig. 418), *Ceratopogon* and *Leptoconops*. All bite man viciously, mostly at dusk or night.

Genus *Culicoides*.—(1.4-1.8 mm. in length). The eyes are large. The antennæ are long and thread-like; the wings contain pigment in the membrane, not scales like mosquitoes. The eggs are white, small and oval, and laid on algae in shallow water. On hatching, the aquatic larvæ wriggle, eel-like, in the water. They are minute, almost colourless and difficult to see. They have four pairs of gills. The pupa is furnished with no exterior casing, so that the wings and legs are fused to the thorax. Two long respiratory trumpets are

present. The adult emerges after three days. *Culicoides austeni* and *C. grahami* have been proved intermediary hosts of *Dipetalonema streptocerca*. They are night biters and prefer dark skins. *C. furens* transmits *Mansonella ozzardi* in Guiana and *C. parvensis* does so in Antigua.

FAMILY CHIRONOMIDÆ

These are midges which look like mosquitoes, but do not bite man. When resting they raise the front pair of legs. The proboscis is vestigial, and there are no scales on the wings. They occur near lakes and rivers in large swarms.

ORDER DIPTERA

FAMILY SIMULIIDÆ

Genus: *Simulium*.

The simuliidæ include "buffalo gnats," black flies and "turkey gnats." Generally small (1 to 5 mm. long), they are blood-sucking, with blade-like piercing female mouth parts, which in the male are more or less rudimentary. Characteristic is the prominent hump caused by strong development of the scutum and reduction in size of the prescutum. The antennæ are composed of ten to eleven joints. In the female the eyes are distinctly separated, but closely set and prominent in the male. The palpi are composed of four joints. The wings are broad and iridescent, with distinct *alulæ*, and the venation is characterized by prominence of the costal veins.

They occur in enormous numbers in favourable localities during late spring and early summer in northern countries, and are particularly abundant in the north temperate and subarctic zones and also in the tropics.

They breed by preference in running water and shallow mountain streams; sometimes in roadside ditches. Both sexes feed on mammalian blood and are extremely voracious, attacking cattle and man. The bites are most painful. In cattle they may cause severe loss of blood and consequent anaphylactic phenomena. Death may result from œdema of the lungs.

The eggs, in masses of 300–500, are laid in water, and are triangular and yellow, becoming black at a later stage. The larvæ emerge in two or three weeks and immediately attach themselves to stones. They are cylindrical, with posterior swollen extremities. In colour they are brown to black—consist of twelve segments. The posterior end is provided with toothed disc-like suckers composed of two modified parapodia. The pupa attaches itself to aquatic weeds; it is encased in a cocoon open at the top from which a pair of branching gills emerge. There are the respiratory filaments attached to the dorsal portion of the thorax. Oxygen is obtained by diffusion through the cuticle. Pupal period is 5–6 days.

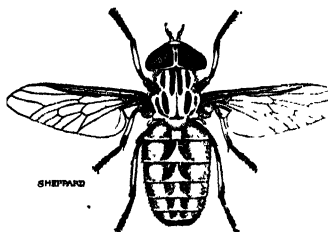
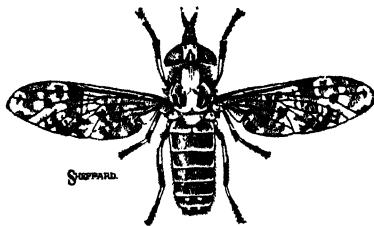
The various species of simuliids in West and Central Africa live under ecological conditions similar to those found in Guatemala. It has been noted that the African species bite low on the body, and there seems to be a relation between the position of the bites and the situation of the adults of *Onchocerca volvulus* which they transmit.

The following species are common in various parts of the world. *Simulium damnosum*, the "jinja" fly of Central Africa (Fig. 419); *S. reptans*, Europe; *S. indicum*, "potu" or "pipsa" fly of India; *S. vittatum* in North and South America; *Eusimulium avidum*, *E. ochraceum* and *E. mooseri*, vectors of *O. volvulus* in Guatemala (p. 761), and the last two in states of Oaxaca and Chiapas, Mexico, where they are known as "mosquito negrito" or "alazan." *S. damnosum* and *S. neavei* (syn. *S. renauxi*) are intermediaries of *Onchocerca volvulus* in Central Africa. The larvæ and pupæ of the latter species are found in Kenya (in cascades of Kipsonoi river) attached to crabs—*Potamon* (*Parahelphusa*) *niloticus*. This is known as a "phoretic association" as in other species in association with pupæ and nymphs of the mayfly.

BLOOD-SUCKING FLIES

Family: *Tabanidæ*.

Horseflies, gadflies and deer flies are large insects with well-developed bodies (10-25 mm.) They are strong fliers, notorious pests of cattle and deer, and readily attack man, especially *Chrysops*. The males feed on vegetable juices, and do not bite warm-blooded animals. The eyes are very large and widely

Fig. 420.—*Tabanus ustus*, ♂ Nat. size.Fig. 421.—*Hæmatopota*, ♀ × 2½.

(Partly after Austen ; by permission of Trustees of Brit. Mus.)

separated in the female, contiguous in the male. The antennæ consist of three dissimilar segments ; the third is usually elongated. The venation of the wings is complex ; the second longitudinal vein is not forked. The family *Tabanidæ* includes gadflies, *Tabanus* (Fig. 420), *Hæmatopota* (Fig. 421), *Pangonia* (Fig. 422), and *Chrysops* (Fig. 423). They are most frequent near water, being semi-aquatic in their breeding habits, some breeding in moist earth, or leaf mould. Eggs are laid near water in layers, and are narrow and cylindrical (1.0-2.5 mm.), vary from 100-700 and are covered with a secretion binding them tightly together. The larvæ are slender and cylindrical, have 11 segments, a head, and taper at both ends. The pupæ resemble those of lepidoptera. Adult flies emerge from the pupa case through a slit along the dorsum of the thorax. The male *Chrysops* does not feed on blood.

The genus *Chrysops*¹ is found all over the world, but all the known and suspected vectors of *L. loa* are limited to Africa. Thus *C. silacea* and *C. dimidiata* are restricted to rain forests.

The breeding places of *C. dimidiata* and *C. silacea* have only recently been discovered in muddy pools along the Kumba River in the Cameroons by Chwatt and Jones. Larvæ and pupæ are cultured by methods described by Crewe (1954).

Chrysops discalis is grey or yellowish-grey ; in the female black spots are seen on the abdomen. The male (8-10 mm.) is predominantly black, with yellowish-grey spots on the abdomen. This fly is a transmitter of tularæmia in Central and North America, where it is a common species.

C. dimidiata (v.d. Wulp) (Fig. 423), a West African species, is particularly abundant during certain times of the year in Nigeria and the Cameroons, and acts as an intermediary of *Loa loa* (p. 1012). In the Cameroons 7.2 per cent. of wild-caught flies harbour this worm. The face and palpi are yellow ; the scutum black with yellow stripes ; the abdomen yellow with a dusky brown tip. The legs are yellow, with dark tibiæ and tarsi. The distal half of the wing is smoky.

C. silacea (Austen) is a common species in West Africa, also an intermediary for *Loa loa* and is found infected with this filaria in the Cameroons. It differs from the former species in having a red or bright orange abdomen and legs with dark-brown tarsi. *C. distinctipennis* also may transmit *L. loa* in the Sudan.

¹ The proposed subgenus, *Kleiniana*, has now been abandoned by Oldroyd (1961).

C. silacea is responsible for transmission of infection from man to man and possibly between man and monkey. *C. longicornis* and *C. langi* normally obtain their blood meals from animals and are mainly responsible for maintaining monkey reservoir of loasis. Adult females of *C. silacea* and *C. dimidiata* are normally canopy dwellers and are day feeders. *C. zahrai*, a newly discovered species, is crepuscular.

FAMILY MUSCIDÆ¹

Reference.—“Natural History of the Tsetse Flies”, by P. A. Buxton (1955)

GENUS *Glossina* (Wiedemann, 1830) “Tsetse Flies.” (Plates IV, V)

These are large, but narrow-bodied flies, 6 to 14 mm long, with a slender proboscis projecting forwards to twice the length of the head, enclosed in inwardly grooved palpi. The wings are long, clear to brownish, with the 4th longitudinal vein curved sharply forwards to meet a short transverse vein. This and the position

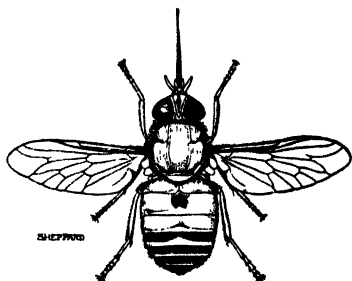


Fig. 422.—*Pongonia rüppellii*, ♀ × 1½.
(Partly after Austen; by permission
of Trustees of Brit. Mus.)

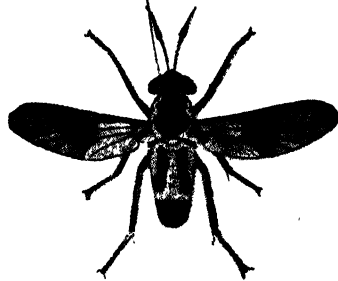


Fig. 423.—*Chrysops dimidiata* (v.d.
Wulp.), ♀ × 2½.

of the wings at rest, overlapping on the back (Fig. 424) are characteristic of *Glossina*, distinguishing it from *Stomoxys* (Fig. 427), *Hæmatopota* or *Chrysops*. The body is dark brown or grey; the abdomen in some species is marked by well-defined dark brown cross bands, interrupted in the middle line, on a buff or grey ground. The proboscis consists of three parts, labrum, hypopharynx and labium (Fig. 425). The bulb of the labium contains muscles which activate a cutting mechanism at its tip. In feeding, the proboscis is inserted up to the bulb, and then withdrawn a little before sucking proceeds. The bite of larger species is exceedingly painful.

Tsetse flies are confined to tropical Africa. Records from the south-west corner of Arabia are doubtful. The two most important species, *G. palpalis* and *G. morsitans*, together cover the greater part of equatorial Africa. The genus comprises twenty-two species, divided by Austen into four groups (see table facing p. 1066). Five species are definitely known to transmit sleeping sickness in the field; seven are concerned in the transmission of animal trypanosomiasis. Many can be shown to transmit various trypanosomes in the laboratory, but are unlikely to act as vectors in nature, because of their habits. To obtain blood the tip of the proboscis is flexed, which enables the blood to be sucked up by “pool-feeding.” People become sensitized to these flies and the reaction is then intense with swelling and wheal formation in response to injection of the insect’s

¹ The Editor is indebted to Dr. Kenneth Morris, D.Sc., F.R.E.S., for considerable assistance in this description of the tsetse flies.

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saliva.
inhibition techniques.

Bionomics.—These flies are adapted to certain conditions which vary with the species; some are just capable of surviving the unfavourable season and a comparatively small change may suffice to tip the balance against the fly, and even modifications in the vegetational cover are effective. Swynnerton laid down that each species needs the concurrence of vegetational types which are necessary for mating, breeding, feeding and sheltering. Hungry flies haunt roads and pathways. They do not live in continued association with herds of game, but rather feed, then fly away to digest their meal. Each species has its own food preference. Their eyes are adapted for detection of movements as distinct from appreciation of form, but scent plays a part in the case of *G. pallidipes*, *G. palpalis* and *G. brevipalpis*. Tsetse flies are dispersed by spontaneous movements along paths and by carriage by cattle and game; there is also automatic dispersal as the result of seasonal expansion, the basis of which is hunger.

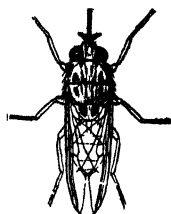


Fig. 424.—Tsetse fly at rest
× about 1½.

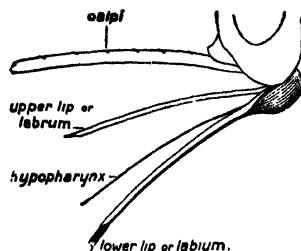


Fig. 425.—Mouth-parts of
Glossina.

Life-history.—The larvæ mature one at a time in the abdomen nourished by secretion from the highly-branched milk glands which ramify throughout the abdomen. They remain in the uterus 10–12 days and, when fully developed, the female selects a suitable place to deposit them. The larva is therefore discharged fully-developed; when fully-grown it is almost as large as the abdomen of the female fly, and is a yellowish ovoid body composed of thirteen segments with two small hooks at the anterior pole and two respiratory protuberances at the posterior end (Fig. 426). It burrows half an inch into loose soil or sand, or conceals itself under dead leaves. Then it rounds itself up, hardens, and the chitinous covering becomes dark brown. After the pupal stage has lasted three to four weeks the fly emerges. The adult female lives 3–6 months, and during this period 6–12 larvæ are produced. A female tsetse deposits the larvæ singly, at intervals of about eight days, choosing a shaded spot, where cover for the pupating larvæ is available in the form of humus, for instance, beneath a log.

Technique of dissection of glossina.—The freshly-killed insect should be placed on a slide with the wings and legs removed. To demonstrate the salivary glands, the fly should be fastened to the floor of a dissecting trough and enough normal saline added to cover it.

Two incisions are then made in the thorax: (1) a median longitudinal from the neck to the end of the abdomen; (2) a transverse incision extending in a line with the bases of the wings, or along the transverse suture. The integument of the lateral walls is severed almost to a point near the attachment of the legs, care being taken not to cut too deeply into the muscular tissues.

A dissecting needle is inserted at either end of the longitudinal slit, and the thorax gently pulled asunder. The muscular tissues are teased out from the anterior half of the thorax and head, leaving the glands attached to the hypopharynx and the labium.

For the removal of the gut, the fly should be placed, vertical surface uppermost, on a glass slide and a drop or two of normal saline added. The integument

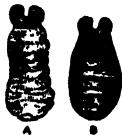


Fig. 426.—A, Larva of *Glossina palpalis*. B, Pupa (After Roubaud.)

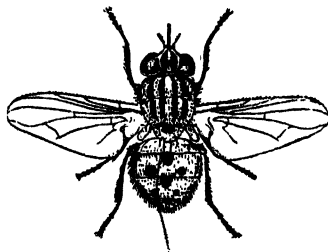


Fig. 427.—*Stomoxys calcitrans*. $\times 3$.

is gently nicked at the sides as near the end of the abdomen as possible. The left hand needle should be placed on the thorax, and the right hand one on the partly severed end of the abdomen. The latter should be gently pulled aside until all the viscera are dragged out.

Species.—The most important vectors of human trypanosomes are *G. palpalis*, *G. morsitans*, *G. tachinoides* and, to a lesser extent, *G. brevipalpis* and *G. swynnertoni*. (Map XII).

G. palpalis, Rob.-Desv.—This has a very wide distribution, throughout West Africa from Gambia to the Congo and eastwards to Lake Victoria. It requires a high humidity (45 to 85 per cent. relative humidity), and temperature 21° – 32° C. which, together with food, influence its distribution. It is not found in tropical rain forest except in clearings around villages, roads and farms, but usually lives close to water. In the savanna country (less than 50" rainfall) it requires the heavy shade found only along water courses. Seasonal distribution is pronounced; it is confined to dense evergreen shade and permanent water (primary foci) in the dry season, spreading widely in the rains to secondary foci of deciduous thickets. Breeding strictly follows this distribution, since exposure to sun or desiccation is fatal to the puparia. It is most partial to man and domestic animals, but also feeds on lizards, monitors, tortoises, crocodiles and hippopotami and feeds mostly at dawn. These seem the main food hosts in West Africa, limiting the distribution to the neighbourhood of human habitations, whereas in East Africa it is able to subsist largely on wild mammalia and reptiles. On large rivers and lakes it constantly moves along the banks and will follow canoes far out, but on small streams or water-holes the fly populations are stationary and congregate around small glades or openings in the bush which constitute feeding grounds. Hence the danger of small clearings around water-holes, paths or villages, which create artificial feeding grounds with maximum opportunities for transmission of trypanosomiasis. Its distribution and marked preference for human food make this species the most potent vector of *Trypanosoma gambiense*. In West Africa it transmits trypanosomiasis of stock also. The subspecies *G. palpalis fuscipes* (inland East Africa to Congo district and Cameroons) is found sometimes 12 miles from water in areas of humid forest interspersed with elephant tracks. It evinces great need for shade and high humidity. On Lake Victoria these flies are carried and dispersed by canoe traffic. The pupae are deposited in shaded sand of the fly beaches, but during the dry

season it contracts its range and may then die out spontaneously. *Sep. fuscipes* is distinguished by special shape of the gonopods; *sep. martinii* (Lake Tanganyika) likewise.

G. austeni, Newst, 1912 (East African coastal district).—This species favours secondary thickets, especially on River Juba in Somaliland, which are more or less evergreen in the dry season. It breeds in fairly dense cover, but may do so in open vegetation and is usually found in miombo forest and thickets, from coast level to 3,000 ft. Reluctant to approach man, it feeds mostly on bush-pigs and wart hogs which supply 88 per cent. of its food. It is active by night and is guided by scent.

G. tachinoides, Westw.—This is found in West Africa north of the coastal and forest zones, also in the south west corner of Arabia. It requires slightly drier climatic conditions than *G. palpalis*, hence its distribution throughout inland savanna, where the primary (dry-season) foci are confined to evergreen bush fringing rivers and lakes with permanent water, from which there is a wet season extension of 5 to 6 miles to secondary foci along temporary streams or pools. It can breed in lighter bush than *G. palpalis*, but shade and proximity of water are essential. It is very catholic in its choice of host and is able to subsist entirely on reptilian blood. It does not form concentrations in the proximity of villages, as does *G. palpalis*, unless this is necessitated by limitations of suitable cover. It is an important vector of *T. gambiense* in the hinterland of West Africa, also of *T. vivax* and *T. congolense* among cattle.

G. morsitans, Westw.—This is widely distributed throughout equatorial Africa, from the Anglo-Egyptian Sudan to Rhodesia in the east, and from Senegal to the Congo in the west. In its western range it is represented by the geographical race or sub-species, *G. morsitans submorsitans*, Newst. It is essentially a tsetse of savanna, where it is widespread, irrespective of the presence of surface water. It is found from sea-level to 5,500 ft. in East Africa. Its climatic requirements are 40–60 per cent. relative humidity and a mean annual temperature of 21° C. It never occurs within evergreen or intermediate forest. Savanna woodland and thorn thickets (the *Isoblerina-Brachystegia* woodland, or “miombo”) form its breeding and resting places, and open grassland and glades between woodland are its feeding grounds. It feeds in the mornings at dawn. It is unable to live in thorn bush, except in regions of high rainfall, but in Ngamiland it prefers the thickest vegetational types, breeding taking place on forest fringes. The seasonal concentration of the fly into dry season foci is less marked in East than in West Africa, where the dry weather climate closely approaches conditions fatal to the fly. It is essentially a game tsetse, dependent on large ungulates for its main food supply, though attacking man and cattle readily when in contact with them. but it has recently been shown that wart-hogs and bush-pigs provide about half its food supply. Within its climatic range, the presence and movement of fly concentrations is governed by those of game. The feeding grounds are small glades or edges of open spaces and its breeding haunts are beneath fallen logs, in hollows between root bases of trees, in rot holes and other dark places. The females travel through savanna more extensively than do the males. The latter seldom live longer than 2–6 weeks; the former twice as long. Moreover the female population is twice as great and they attack man when fly density is at its lowest ebb. Both races, *G. morsitans* and *G. submorsitans*, disperse when rains commence, but the longer rainy season in Tanganyika results in much more extensive dispersal than occurs in Nigeria. It tends especially to attack moving objects, following game, cattle or humans for miles. This, and its habits of entering cars or trains passing through a fly-belt, brings the fly into towns and villages, and also causes spread into new districts, though it is not partial to human blood. The increase and spread of *G. morsitans* is

alarming in many parts of East Africa and has caused wide desolation through loss of cattle: 200,000 sq. miles of Tanganyika have been rendered unproductive through the presence of this and the following two species. Its spread is one of the main agricultural problems of Tanganyika, Nyasaland and Northern Rhodesia. It carries *Trypanosoma rhodesiense*, cattle and game trypanosomes, especially *T. brucei*.

G. swynnertoni, Austen.—This has a local distribution in Tanganyika and just into Kenya, but is of considerable importance as a vector of trypanosomes of both man (*T. rhodesiense*) and cattle. It was involved in an outbreak of sleeping sickness in Mwanza Province, Tanganyika (see p. 119). A savanna tsetse and a game feeder (the main food hosts are kudu, roan antelope, giraffe and pig), it yet freely attacks man, domestic animals, monkeys and rodents, and so cannot be controlled by game eradication. It is said to be the only species which is found in houses. It is found up to 6,000 ft. and breeds mainly in thickets with a rainfall of 16–30 in. This species is readily controlled by applications of gammexane at 14-day intervals.

G. pallidipes, Austen.—This has a wide distribution in East Africa, Italian Somaliland, Uganda, Kenya, Tanganyika, Nyasaland, Northern Rhodesia and Zululand. It requires a slightly higher humidity than *G. morsitans*, and occupies dense savanna forest and secondary forest. It is a game feeder and an important vector of cattle trypanosomes and feeds in the evenings. Its presence renders useless 1,250 sq. miles of fertile grazing in the Masai reserve and 3,000 sq. miles, or half the territory, in Zululand. It is found up to 6,000 ft. Humidity is a factor in the activity of this fly.

G. longipalpis, Wied.—This is the West African representative of *G. pallidipes*, occurring from Senegal to the Cameroons, in secondary forest, coastal savanna and dense savanna forest inland. It does not enter tropical rain forest. It subsists mainly on smaller antelopes, and is a vector of cattle trypanosomes. It has occasionally been found naturally infected with *T. gambiense*.

G. brevipalpis, Newst.—This has a wide distribution from Abyssinia to Zululand and westwards to the Belgian Congo, and a similar habitat to *G. palpalis*, in gallery forest and dense secondary forest, but it can stand slightly drier conditions. It lives on mammalian hosts, and frequently attacks man, cattle and pigs. It may transmit both sleeping sickness (*T. gambiense*) and nagana (*T. brucei*).

G. longipennis, Corti.—This is found throughout the dry savanna and thorny scrub belt of East Africa, from the Southern Sudan and Italian Somaliland, through Kenya to Tanganyika. It is not known to have been associated with any outbreaks of human or animal trypanosomiasis, but feeds mostly on rhinoceros.

G. fusca, Walk.—This is confined to forest regions of West Africa. Its activity is crepuscular, with a preference for horses and cattle rather than man. It has been found infected with the trypanosomes of nagana (*T. brucei*).

G. fuscipleuris, Austen.—This is the East African representative of *G. fusca*, occurring in forest and gallery forest of the Eastern Belgian Congo and country around Lake Victoria. It tends to attack man and domestic stock, and is known as a plague in the Masai reserve through its exceedingly painful bite which stampedes cattle. It transmits nagana (*T. brucei*).

G. pallicera, Bigot.—This is distributed fairly widely through West African rain forest. It rarely bites man, is little noticed and unlikely to be involved in the transmission of human trypanosomiasis.

Control measures.—Early diagnosis and treatment of cases of sleeping sickness are essential, and especially "mass treatment" by mobile teams, examining and treating the total population, village by village, but mass treatment alone, without simultaneous entomological measures, has, as in French West Africa, failed to eradicate sleeping sickness.

Entomological.—The only effective measure, so far devised, is an alteration of habitat by clearing. Two types are used: (1) eradivative, aims at extermination of the complete fly community by removing essential plant associations of all primary foci over a large district; (2) protective, to reduce contact between fly and man by removing all fly-belt vegetation from around villages, road and river crossings, water-holes, etc. A minimum of 440 yards on each side of the object is considered necessary for *G. palpalis* and *G. tachinoides*, but this method is useless against *G. morsitans* group. Protective clearing at best is an unsatisfactory palliative and is apt to go wrong, whilst bad clearing may make the conditions worse than before. Before clearing it is essential to have accurate knowledge of the species of glossina involved and its exact habitat, and a detailed study of the botany of the fly-belt now shows that the fly can be exterminated by removal of a few definite species of tree.

The preparation for this kind of work consists of a vegetational, agricultura and tsetse survey and selection of lines for isolation barriers to enclose blocks of tsetse-infected bush and should consist of (a) naturally open spaces, (b) bush-types sufficiently wide, unsuited for the tsetse concerned, (c) continuous wide thicket for *G. morsitans* and *G. swynnertoni*.

In East Africa the four important species to be guarded against are: *G. morsitans*, *G. swynnertoni*, *G. pallidipes* and *G. palpalis*.

The presence of man appears to repel *G. morsitans*. Great advances have been made in the methods of reclaiming land, especially in Tanganyika. In order to convert fly-bush to cultivation steppe definite lines should be made in which the bush is cut back and cleared. In thorn savanna infested with *G. swynnertoni*, discriminative clearing is satisfactory, but in plains adorned with lace-work of vegetation infested with *G. swynnertoni* and *G. morsitans*, a clearing of one mile wide should be made along the edge of the thorn bush. By these methods during the last twenty years some 1,000 square miles of Tanganyika have been freed from tsetse. (Nevertheless two-thirds to three-quarters of the land is still infested. In Kenya the figure is about one-seventh and in Uganda one-fifth.) For the results of DDT, see p. 861.

Survival rate.—Marking methods for use in the field have been devised and by analysing the recapture of the released adults, the mortality rate has been calculated for a number of species. In Tanganyika *Glossina morsitans* has a weekly mortality rate of 28 per cent. in the female and 38–69 per cent. in the male. The average life of the male is shorter in the dry than in the wet seasons. In other species, although the sex ratio at emergence from the pupa is equal, females come to predominate over the males in the adult population.

Traps.—Harris claimed considerable success in Zululand with a tsetse fly trap, the material for which costs about 30 shillings. This is designed to resemble a cow or antelope and consists of a framework of light wood, covered by hessian cloth roughly triangular in section, with a flat top, 6 ft. long by 3 ft. wide, the sides converging to about 3 in. apart, with a narrow open slit at the bottom, the ends being vertical and triangular. The body is slung on wires, so that the open slit is 48 in. from the ground. To the flat upper surface a transparent cage of wire gauze, of a mesh sufficient to retain a fly, is fixed.

Where the cage fits to the flat surface, the cloth is removed and the wire so arranged that the flies cannot return to the hollow body of the trap.

These traps are then suspended on the sunny margins of evergreen bush haunts of the flies, and so placed that they throw a separate shadow, and it has been found that, in suitable weather, each trap will kill 100–200 flies daily. This type has been successful with *G. pallidipes* and *G. palpalis*, but is not so with *G. morsitans*. The single screen (S.S.) trap is excellent for *G. palpalis* and *G.*

pallidipes, and where suitable climatic conditions prevail, *G. morsitans* is attracted, but these traps have been found useless in Southern Rhodesia.

Swynnerton employed a similar trap, containing a live calf, to which the flies are attracted by scent. The most effective is a moving screen carried by fly-boys, who are able to catch with a net every fly that the screen attracts. Hand catching is effective in small isolated fly-belts. Tanglefoot spread on clothes or on shields or screens protects labourers from being bitten. An attempt to introduce a sterile race of tsetse has been made by Vanderplank, who crossed *G. morsitans* with *G. swynnertoni*, and the cross-mating produced fewer pupæ. The male hybrid inseminate females, but there have been no offspring, whilst attempts to cross female hybrids with pure-bred males of both species have failed.

In West Africa operations have been directed against *G. palpalis* and *G. tachinoides*, but the most important is connected with the Anchau settlement in Nigeria. This has entailed surveys, the construction of roads, clearing 110 miles of stream, sinking of wells, study of local soils and vegetation, agricultural experiments, investigation of native farming methods, census, monthly fly surveys, and construction of new settlements. Two other campaigns of protective clearing have been carried out in Nigeria in 1938 in Katsina and Zaria.

By these means it is estimated that 200,000 people have been protected against infection. Large-scale experiments in eradication of these two species from the savanna forest of the northern territories of the Gold Coast are also in hand. Removal of trees and shrubs concerned throughout the whole river system has resulted in the disappearance of these flies, especially in the Lawra district in the northern territory drained by the Kamba river.

"Rod clearings," in the West Nile district of Uganda especially, are used for the control of *G. palpalis fuscipes*, extend 10 yards in width on either side of the river and project 800 yards in length, with the village or road crossing in the centre. The grass is kept short.

Grass-firing.—Nash advises against this measure which is commonly practised in the dry season as favouring the spread of tsetse. Prohibition has resulted in the reduction of the *G. morsitans* population in Tanganyika, which may be due to the destruction of pupæ by ants.

In Northern Nigeria climatic conditions are so severe that destruction of woodland by fire exclusively reduces shelter needed by *G. morsitans*, but there is no evidence that it diminishes the *G. pallidipes* population.

Barriers.—Thickets of the *Burttia-Baphia* type may be dense enough to form an effective barrier against *G. swynnertoni* as these flies will not cross them, but they need to be more than one mile wide to prevent them from drifting through during the leafless season.

Afforestation with evergreen thicket, as on the edge of a deciduous barrier, can be considered as a measure against the advance of *G. morsitans*.

In Tanganyika it has been shown that a thicket barrier consisting largely of *Euphorbia terucalli*, 100 yards deep, impedes the passage of *G. swynnertoni*.

Symes's block method is mainly devised for *G. palpalis*. Blocks of riverine bush, about two miles in length, are separated by clearings made 1,000 yards wide. Paths are made along the river banks and these are patrolled by catchers with nets. In one block hand-catching reduced the numbers caught from over 5,000 in three months to seven in five months in 1935. Along the shores of Lake Victoria the block method, combined with hand-catching, has been instrumental in reclaiming 16 square miles of land, and similar methods have been successful along the rivers in Kenya and S. Sudan.

Game control.—The arguments in favour of control by killing off game came chiefly from Rhodesia and Bechuanaland, where *G. morsitans* is concerned.

It is claimed that anti-tsetse measures should include game control, not to the limit of extermination, but by rigid control. Buffalo and wildebeeste should be declared vermin. In Southern Rhodesia it is claimed that effectiveness is established on these lines: (1) reduction of game along the edge of fly-free country; (2) creation of a game-free zone, 10 miles or more wide, beyond farm boundaries; (3) control of motor traffic, of hunters and prospectors. By these measures in 1940 and 1941, 36,000 wild animals were shot and the position was greatly improved.

From French West Africa come arguments against game destruction. There is no evidence that big game, in a wide sense, can be reservoirs of *T. gambiense*, and at best constitute only a minor one for *T. rhodesiense*. Irradiation of these flies with radio-active isotopes, radio-active iodine and phosphorus is now under trial at Harwell on the same principles as *Dermatobia* (p. 1079). The results are awaited with interest. The method depends on the well-known sensitivity of reproductive tissues to radiation. Doses of about 5,000 *r* (ten times the dose lethal to most mammals) can be given to insects in the pupal stage without greatly curtailing their lives, but the resulting adults are generally sterile. The females of most insects allow only a single mating, and if this has been with a sterile male the act is sufficient to prevent reproduction.

Social.—Segregation of infected people and movement of the population out of infected areas may be used as a last resort in severe outbreaks, or where other control measures are impracticable. Control of travellers passing through sleeping-sickness zones must be instituted. The spread of the *morsitans* group of flies has been prevented by passing traffic through a cleansing chamber on leaving a fly-belt. Re-population and development of cleared areas inhibits re-growth of fly-belt vegetation and re-entry of the fly. Siting new villages at primary foci of the game tsetse, after initial measures against the fly, has successfully broken up large fly communities.



Fig. 428.—*Musca domestica*, ♀ × 4.

MUSCIDÆ THAT DO NOT SUCK BLOOD

Family: Muscidæ.

Genus: *Musca*.

The common housefly (Fig. 428), *Musca domestica*, is a domestic species; on account of its insanitary habits it acts as a vector of pathogenic micro-organisms, especially dysentery bacilli, cysts of *Entameba histolytica*, other intestinal protozoa and helminth eggs.

M. domestica (8 mm. in length) is dark grey, with four parallel black stripes on the dorsum of the thorax. Eggs are laid in masses in manure and other refuse, hatching in twenty-four hours in hot weather. The larvæ are legless maggots with large stigmal plates, bearing posterior spiracles on the abdomen. Pupation under favourable conditions occurs in five days. The puparium is an elongated

barrel shape, and in the tropics the pupal stage lasts three days. The adult fly lives about one month. Larvæ are capable of traversing considerable thicknesses—over 3 feet—of soil in order to reach the surface. In the tropics houseflies are in evidence throughout the year; in dry deserts they die off during the hot season. In temperate zones they perish in the winter season, but are most numerous in the early autumn. Larvæ survive the winter buried in decaying vegetable matter. The best method of storing manure is to ram it so tight that fermentation is intense enough to destroy maggots.

The nematode worm, *Habronema muscæ* (stomach-worm of horses), is ingested by *M. domestica* in its egg or larval stage, and the embryo continues its development in the body of the fly, so that the final stage is found in the proboscis of this insect.

FAMILY: SARCOPHAGIDÆ (Flesh flies)

"Blowflies" include blue-bottles, green-bottles (*Calliphoridae*) and flesh flies (*Sarcophagidae*). The larvæ usually feed on dead animals. These flies are primarily scavengers.

Wohlfahrtia magnifica (Schiner, 1862), the principal sheep-maggot of South Europe, measures 10–13 mm., and is ashy-grey, with black legs. The abdomen is light-grey with three black spots on each segment. This species is found in



Fig. 429.—Stigmata of muscid larvæ, a means of rapid identification.

Magnified.

Russia, and thence to Egypt and Asia Minor. In man, larvæ are found in open wounds, nasal fossæ, palate and eyes (see p. 835). The larvæ of these various flies are identified by the shape of the posterior stigmata. (Fig. 429.) The corresponding species in N. America is *W. vigil* Walker, the larvæ of which are found in superficial swellings of the head and neck.

Family: Calliphoridae.

Chrysomya bezziana (Villeneuve, 1914) is metallic blue with a bright-green thorax. The male has reddish-brown eyes closely approximated, and deep orange antennæ. The larva (12 mm.) is yellowish-white, with slightly pigmented extremities. Eggs are laid in diseased tissues whilst larvæ in wounds cause great destruction of tissues in India and Cochin-China.

Cochliomyia (Callitroga) hominivorax (Coq., 1858), syn. *C. americana* (Fig. 430), the "screw-worm" fly, is common throughout America as an obligatory flesh-breeding fly. It was originally thought to be the same as *C. macellaria*, which

is essentially a carcass-breeder and is the common American form. It is greyish, with three well-marked dorsal stripes, and measures 9–10 mm. It lays masses (300–400) of eggs on the surface of wounds, in ears and nasal fossæ, and from there

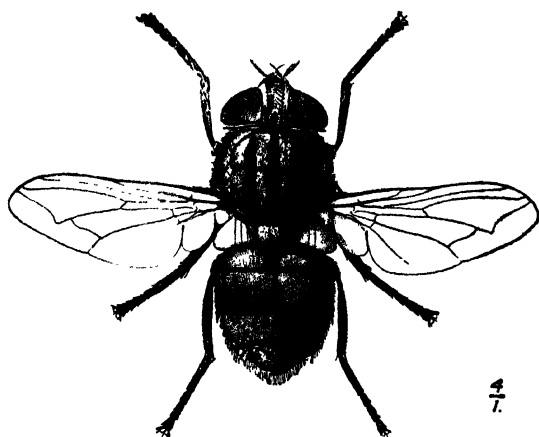


Fig. 430.—*Cochliomyia hominivorax*, female.
(some entomologists regard *Callitroga* as the correct generic name)



Fig. 431.—*Cochliomyia* (*Callitroga*) *hominivorax*, larva. $\times 5$.

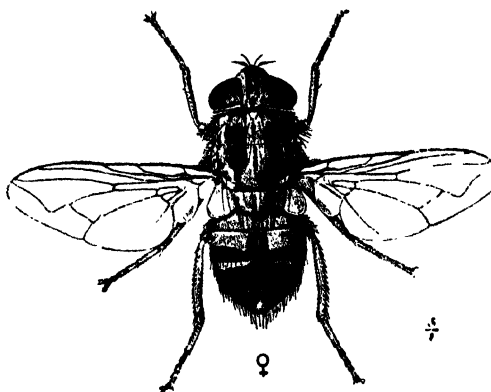


Fig. 432.—*Cordylobia anthropophaga*.

larvæ are hatched in a few hours. The larva (Fig. 431) is white, $\frac{3}{4}$ in. in length, and formed of twelve segments, with circles of minute spirally-arranged spines giving it a screw-like appearance. The larvæ burrow into tissues, destroying

cartilage and bone. Ear or nasal fossæ may be attacked, and the brain may be penetrated, causing death.

Cordylobia anthropophaga (Grünberg, 1903) (Fig. 432), the Tumbu Fly or "Ver du Cayor," is widely spread in Central Africa. It measures 8.5 to 11.5 mm., and is yellowish-grey, with black spots on the abdomen and brown wings, and resembles *Auchmeromyia luteola*. The male *Cordylobia* is distinguished from the male of *A. luteola* by its closely-set eyes. In the female *Cordylobia* the abdominal segments are of equal size, while the female *Auchmeromyia* has a triangular abdomen with the second segment long. They differ in life history and habits. *Cordylobia* is an obligatory myiasis producer and gives rise to lesions in man or animals. Usually, it is inactive; when disturbed, it flies away with great rapidity. The eggs, white and visible to the naked eye, are laid on the ground, or on clothing if it is contaminated by urine or sweat. Larvæ are activated by the warm body of the host, and in the early stages are provided with structures, such as cuticular spines to assist penetration of the skin. There are three moults or instars (Fig. 433). Development in subcutaneous tissues is

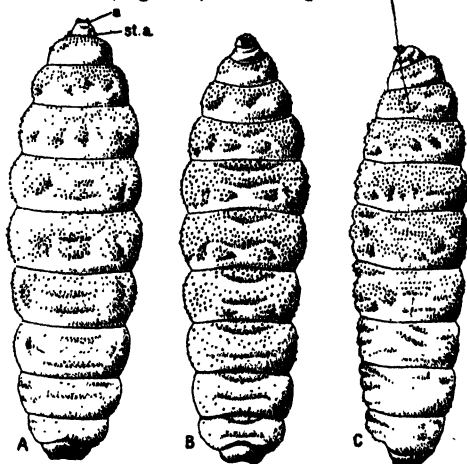


Fig. 433.—Adult larva of *Cordylobia anthropophaga*.
× 5. (After Brumpt.)

A, Dorsal view; B, ventral view; C, lateral view.
a, Antennæ; st. a., anterior spiracle.

completed in twelve days. The cavity containing the larvæ breaks down to form a swelling, resembling a boil which bursts without much inflammation. The larvæ emerge from the swellings (Fig. 246, p. 836), which are situated on the forearm, scrotum, and other parts of the body; they fall to the ground and pupate in thirty-six hours. The pupa has a characteristic shape with a square truncated extremity. Pupal cases are commonly found in rat holes. The adult hatches in 10–20 days according to the temperature prevailing.

Larvæ can be extracted by pouring water over the hole in the skin, thus stopping their oxygen supply; they then extend their posterior spiracles, and can be squeezed out.

The Tumbu fly provides a remarkable example of metazoan immunity. In guinea-pigs the degree of immunity produced by previous infection is not general, but local. No antibodies are present in the serum. Larvæ penetrating into the immune area die in forty hours, while immune skin grafted on a non-immune animal retains and imparts its immunity (Blacklock and Gordon).

Auchmeromyia luteola (Fabr., 1805) (Fig. 434) is widely distributed throughout tropical Africa, from Northern Nigeria to Natal, and also in Southern Sudan, in latitudes from 18° N. to 26° S. from sea level to 7,500 feet in dry or wet climates. Its general colour is orange-buff, but numerous small black hairs impart a smoky appearance. It measures 10–12 mm. with a stoutly-built body. The head is large, with the eyes well separated in both sexes. The thorax shows

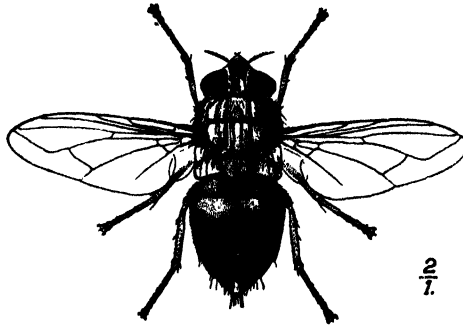


Fig. 434.—*Auchmeromyia luteola*, female.

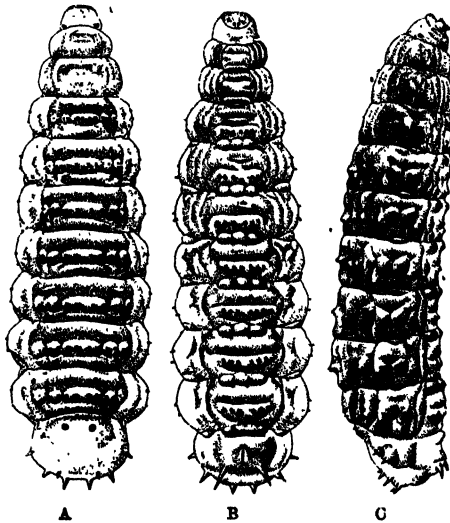


Fig. 435.—Larva of *Auchmeromyia luteola*. $\times 5$. (After Brumpt.)

A, Dorsal view; B, ventral view; C, lateral view.

two indistinct, dark, longitudinal stripes. The abdomen differs in the sexes, the second segment in the female being twice the length of the same segment in the male. In the female the dark band on the second segment is so wide that it occupies almost the whole (Fig. 434). The third segment is almost black in both sexes. The wings are smoky-brown with conspicuous venation. Human and simian faeces constitute the most important source of food. First batch of eggs is laid 2–3 weeks after emergence. The larva (Fig. 435), known as the "Congo floor-maggot," is dirty white, semi-transparent, 15 mm. in length, and composed of

11 segments. The central part of its ventral surface is flattened. At the posterior margin of each segment are three short limbs, transversely arranged, provided with backwardly directed spines which enable the maggot to move about like a caterpillar. The anterior segment is roughly conical and bears a mouth which is placed between two black hooks protruding from the apex and curving backwards towards the ventral surface. Paired groups of minute teeth are placed around two hooks, forming a sort of cupping apparatus. There is a remarkable dorsal diverticulum, corresponding to the food reservoir of the muscid larva which opens into the cesophagus near the anterior end.

After the larva has fed it forms a conspicuous red object filled with blood. After taking its meal it retreats into the cracks in the floor from which it emerged. It feeds by scraping with the mouth-hooks until it reaches a blood-vessel. The first segment is then retracted and the sucker apparatus applied as in wet-cupping. The host must be hairless and remain quiet, e.g., a man asleep. It also attacks the ardvark (anteater) and nestling birds. Larvæ are frequently found under the mats on which natives sleep and in the earth at a depth of 3 in. They feed mainly at night, and drop off at once if disturbed. They can be recognized by the characteristic shape of the stigmata or openings of the respiratory tubes (Fig. 429).

When ready to pupate, the larva selects a suitable spot, and lies dormant. The puparium is a dark, reddish-brown, oblong body, 9-10.5 mm. by 4.5 mm. This stage lasts from two to three weeks.

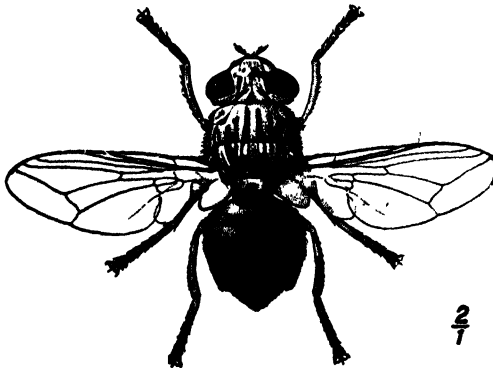


Fig. 436.—*Dermatobia hominis* (Linn Jr.) syn. *cyaniventris*, female.

The adult fly (Fig. 432) is usually found sitting motionless amongst the thatch, beams and cobwebs of the walls and roofs of native huts and, on account of its protective coloration, is difficult to detect. It deposits its eggs in the crevices of the floor, particularly mud-floors, in spots where urine has been voided. To avoid being bitten, travellers should sleep on beds or in hammocks. Bites are painless.

FAMILY: CHLOROPIDÆ

These are Hippelates flies, members of the family Chloropidæ (*Oscinidæ*) and commonly known as "frit flies." Small members are known as "eye flies" because of their liking for the lacrymal and sebaceous secretions, and also for blood and pus. They are extraordinarily persistent in their attentions.

Siphunculina funicola, the "eye fly" of India, Ceylon and Java, is responsible for the spread of conjunctivitis. It has been shown by Roy that the seasonal prevalence of this fly in Assam closely coincides with that of epidemic con-

conjunctivitis, and there is a similar belief for an allied species in Southern United States. In parts of California these flies are a veritable pest.

Hippelates papillipes has been suspected of transmitting yaws in Jamaica (p. 565). They are small black flies with aristate antennæ. The eggs are deposited on decaying organic matter and the larvæ feed on the same material.

H. pusio, known as the "eye gnat," or "*mal de ojo*," is particularly abundant in Florida and causes great annoyance to men and animals.

FAMILY: OESTRIDÆ (Bot-Flies)

The inclusion of the genera—*Dermatobia*, *Hypoderma*, and *Gasterophilus* in the family *Oestridæ* is not regarded as strictly correct by most entomologists, but it is convenient.

These are non-blood-sucking flies with primitive mouth-parts, parasitic on animals and man during their larval stages. Cases of ophthalmomyiasis of man have been ascribed to the larvæ of head maggots of sheep and deer. Cases traceable to *Oestrus ovis* and *Rhinæstrus purpureus* have been reported (p. 835).

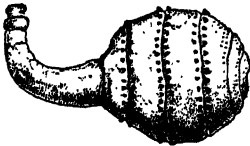


Fig. 437. — *Dermatobia hominis* larva: early stage. (Blanchard.)



Fig. 438.—*Dermatobia hominis* larva: later stage. (After Brauer.)

Dermatobia hominis (*cyaniventris*) (Macquart, 1843) (Fig. 436), "ver macaque" or "macaw-worm," is widely distributed throughout South America. The larva occurs in the most diverse animals: cattle, pigs, dogs, agouti, jaguar,

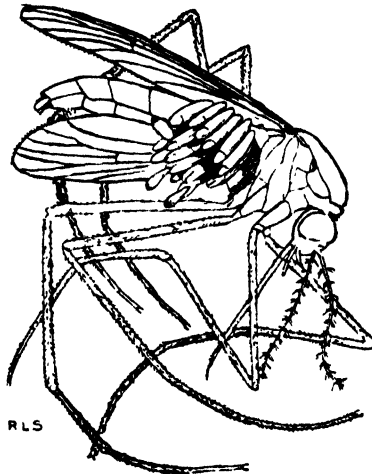


Fig. 439.—*Psorophora* (*Janthinosoma*) *lutzi*, carrying eggs of *D. cyaniventris*. (By courtesy of Tropical Diseases Bureau.)

South American monkeys and birds; it is rare in the mule and never found in the horse. It can complete its development in man and is an example of "obligatory cutaneous myiasis." In man it is found in the head, arm, back,

abdomen, thigh and axilla. When the larvæ are hatched out they penetrate the skin and produce an inflamed swelling about the aperture of entrance, from which exudes a sero-purulent fluid containing the dark fæces of the larvæ. At an early stage the larva has the curious appearance depicted (Fig. 437) and is known as "ver macaque"; and later, when larger (Fig. 438), it is called *torcel* or *berne*. This myiasis is acquired in a curious manner. On attaining maturity, *D. cyaniventris* lays eggs on wet leaves in damp places where mosquitoes feed, especially *Psorophora (Janthinosoma) lutzi* (Fig. 439). Other species can take on this function:—mosquitoes: *Psorophora posticata*, *P. tovari* and *Gældia longipes*; flies: *Sarcophaga terminalis*, *Musca domestica*, *Stomoxys calcitrans*; and a tick, *Amblyomma cajennense*. Packets of eggs are enclosed in a cement which, becoming softened by moisture, adheres to the arthropod's thorax, and the eggs are thus conveyed to man or other vertebrates when the mosquito next feeds. This process is known as "phoresis" or hitch-hiking. The eggs develop, and the larvæ, attracted by warmth when the insect feeds, burrow into the skin and develop like cordylobia. In Brazil this pest has been completely controlled by insecticides—DDT, BHC and toxaphene. (Chap. LII) In Curacao this fly

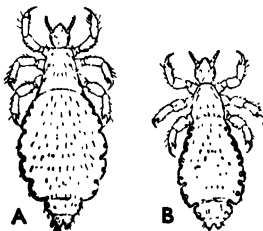


Fig. 440.—*Pediculus humanus*.
× 5. (After Bruce Cummings; by permission of Trustees of Brit. Mus.)

A, *P. humanus*, ♀.
B, *P. humanus* var. *capitis*, ♀.

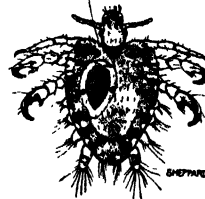


Fig. 441. — *Phthirus pubis*, ♀, showing contained ovum.
× 12.

has, in the space of two years, been exterminated by irradiating the males which, in turn, have sterilized the female flies.

Hypoderma, the cattlegrub, or "ox warble," has the ox as its normal host; man is very occasionally parasitized, producing "larva migrans" (p. 836). Two well-known species are *H. lineata* and *H. bovis*, 13–15 mm., widely distributed in Europe, Asia and North America. The eggs of both species are deposited on the hairs of cattle, hatching within a week. Small larvæ then crawl down the hairs and bore into the skin. This pest can be controlled by rotenone washes and application of rotenone ointment to the larval cysts.

Horse bot-flies, *Gasterophilus*, *G. intestinalis*, *G. nasalis*, especially *G. hæmorrhoidalis*, sometimes attack man, the larvæ burrowing under the skin, causing a creeping eruption. Larvæ are picked up by handling horses, though there is evidence that the fly can actually introduce its eggs directly under the skin. These flies are somewhat smaller than honey bees, with small antennæ sunken in pits. They are strong fliers. Larvæ live in the stomach and intestines of horses. Eggs are deposited on hairs.

ORDER: ANOPLURA (LICE)

Family: Pediculidæ.

Genus: *Pediculus*.

Lice are obligatory parasites and spend the whole of their life on the body of some particular host. They cannot live, apart from their host, longer than

12 hours at 40° C. or 10 days at 5° C. There is a great reduction in the size of the eyes and antennæ. They have flattened bodies without wings, and an indistinctly segmented thorax. The integument is tough, to resist pressure. The number of abdominal segments ranges from six to nine, the last being bilobed. Spiracles stand out prominently on the sides of the abdominal segments. In the male the abdomen ends bluntly, bearing a spine-like penis. The legs are modified for holding on. The eggs, or nits, adhere to the body hairs of host, and the young which emerge are miniature editions of the adults. The species of louse parasitic on man are two in number: *Pediculus humanus corporis*, the body-louse, and *P. humanus capitis*, the head-louse (Fig. 440). These interbreed and produce fertile offspring. The egg nits of *P. corporis* are laid on the body hair, but mostly on the inner surface of clothing. Those of *P. capitis* are laid on the head at the base of the hairs, which grow up with them. The female produces about five eggs a day and continues to do so for a month; the eggs hatch in eight days at 32° C., but take longer at a lower temperature. The immature louse, or nymph, moults three times, and becomes mature in fourteen days. Like the adult, it feeds on blood twice a day. The life span of the adult is from four to six weeks. Lice cannot live for any length of time on discarded clothing. Under experimental conditions they can survive at the low temperature of 5° C.

Infection with lice occurs through close contact with verminous persons huddled together. Lice avoid light, and tend to leave patients with fever and sweating, so that this is a factor in the transmission of disease. They also leave a body which is undergoing hard physical exercise.

Lice convey relapsing fever and the rickettsia of exanthemic typhus (*R. prowazeki*), and that of trench fever (*R. quintana*). They also play a part in the spread of tæniasis. *Dipylidium caninum* is occasionally found in children and has as its larval host *Trichodectes canis*, the dog louse, and it may also develop in *P. humanus*.

The third species is *Phthirus pubis* (Fig. 441), the "crab-louse," which lives chiefly in the genital and inguinal regions, and is acquired mostly during coitus. It is distinguished from other lice by its broad flat body and festooned abdomen of six segments. The second and third pairs of legs have massive talon-like claws. By these means the louse clings to two approximated hairs 2 mm. apart. The life cycle is completed in 27 days.

The lice of rats and pigs—*Hæmatopinus* and *Polyplax*—also belong to this order.

Prophylaxis.—For destruction of lice in clothes on a large scale the most efficient method is by dry or moist heat; a temperature of 50–55° C. will kill in forty minutes. The application of a hot iron to the seams is useful. For practical purposes, clothes should be exposed to 70° C. for thirty minutes. Attention must be directed to folds and pleats.

For head lice the hair must be cut short, and a comb with square-edged teeth (*Sacker* patent), used with soft soap, is useful to remove nits. For destruction of adult lice all former methods have now been superseded by DDT or "neocid," and for details Chapter LII, p. 860, should be consulted.

ORDER: HEMIPTERA (BUGS)

Family: Cimicidæ.

Genus: *Cimex*.

Bed-bugs (*Cimex*) have a world-wide distribution. The species parasitic on man are *Cimex lectularius* (Fig. 442), the bed-bug of Europe, and *C. hemipterus* (*rotundatus*), the bug of the tropics, which is distinguished by its elongated, narrow

abdomen (Fig. 443). In West Africa a species of another genus—*Leptocimex boueti*—attacks man. The body of *C. lectularius* is broad and flat, the head short and broad, attached to the thorax, the antennæ four-jointed, and the eyes present, but reduced in size. The mouth parts (jointed proboscis) are normally folded back under the head. The maxillæ are serrated at the tip. Lying in a groove between the head and the thorax are short pad-like hemi-elytra characteristic of the practically wingless condition. *Cimex* feeds only on blood, and can resist starvation well. The labium does not pierce the skin, but buckles up like that of a mosquito. The bodies of bugs give out a nasty, pungent odour. Bed-bugs are nocturnal in their feeding habits, hiding in crevices during the day-time. The eggs are shaped like a wine-bottle with a cap, and stuck on to the surface of the crevices of woodwork in houses, beds, mattresses, behind pictures and nail holes. Nests can be located by finding the black faeces round holes.

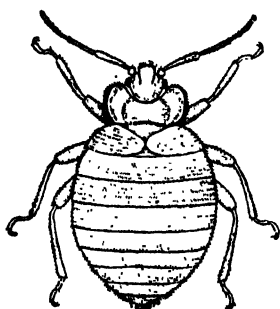


Fig. 442.—*Cimex lectularius*
× 7.

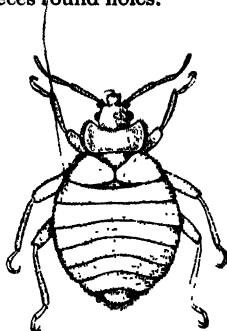


Fig. 443. — *Cimex*
hemipterus (*rotund-*
atus). × 6.

The females deposit eggs in batches from 10 to 50, totalling 200–500: they are large, yellowish-white, and easily visible to the naked eye. The nymphs resemble adults, and are white, with no elytra or rudimentary wings; they mature in about six weeks, if fed at each stage, but each can resist starvation for two months. Under less favourable conditions, development may be protracted to six months or more. Adults may live for many months. Bed-bugs are sensitive to high temperatures: even 100° F. with a fairly high humidity will kill many. The most effective method is fumigation with sulphur. The dosage necessary varies from 12–26 ounces per 1,000 cubic feet, with an exposure of at least six hours. Sulphur dioxide is cheap and, owing to its smell, free from hazard. It kills the active stages of the bug, but a few eggs may escape, and complete combustion must be ensured.

Hydrocyanic-acid fumigation is very efficacious, but dangerous, and must be carried out only by skilled persons. For articles of furniture, which cannot be boiled in water, an emulsion of petroleum is used: 3 parts of soap to 15 of hot water, to which 70–100 parts of oil are added, should be forced into cracks and crevices with a brush.

Coal-tar naphtha is lethal to bugs and nymphs, but less so to eggs. The concentration which can be obtained at 60° F. is 0.2 per cent. over a period of twenty-four hours. Bugs are also readily destroyed by DDT (see p. 859).

Though bed-bugs cause a great deal of irritation by their bites, they have not been actually proved to disseminate disease, with the doubtful exception of relapsing fever, as the experiments of Rosenholz (1927) seemed to show.

FAMILY: REDUVIIDÆ

Reduviid bugs ("Assassin bugs") include a number of species which feed on human blood, inflicting painful bites. They are classified into four genera—*Panstrongylus*, *Eratyrus*, *Triatoma*, and *Rhodnius*, and are confined to America, from 41° N. to 41° S. One (*T. rubrofasciata*) has a cosmopolitan distribution.

These bugs live entirely on wild animals in nests and burrows, but certain species become domesticated. Larvæ and nymphs are flightless, and can only bite human beings in their immediate vicinity, but the adults of both sexes can fly considerable distances. When engorged with blood after a feed they void from the cloaca into the bite a white or dark fluid and by this method *Trypanosoma cruzi* is transmitted. The bite is not infective. Eggs are laid singly.

The larvæ, on emerging, engorge themselves with blood on four occasions, undergoing a moult after each; they then become nymphs, which, after several feeds, moult for a fifth and final time before becoming adult. The whole cycle of evolution takes three or four months to complete.

The life-span is on an average one of three months, and when once infected with *T. cruzi* the insects remain so for the remainder of their life span.

PANSTRONGYLUS (Burmeister, 1835) AND TRIATOMA (Wolf, 1802)

The genera *Panstrongylus* and *Triatoma* were separated by C. Pinto (1931) on certain characteristics of the probosces and antennæ.

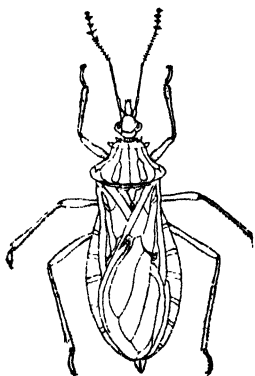


Fig. 444.—*Panstrongylus megistus*.
Nat. size.

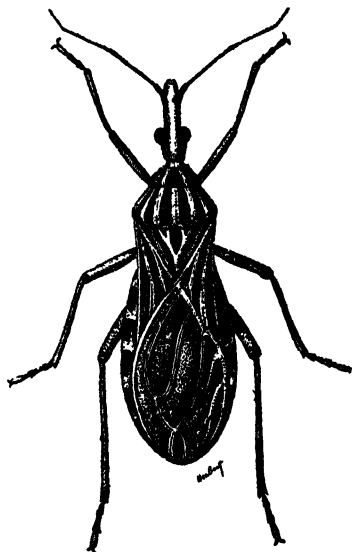


Fig. 445.—*Rhodnius prolixus*, adult male.
× 2½. (After Brumpt.)

GENUS *Panstrongylus*

Synonym.—*Conorhinus* (Laporte, 1832).

This genus is distinguished by its smooth body and elongated or conical head. *P. megistus* (Burmeister, 1835)—Brazil—is a domestic species measuring 3 cm. in length. The body is black, with red stripes. (Fig. 444.) The insect has feeble powers of flight. The life-cycle takes a year to complete, and the adults can live about six months.

P. chagasi (Brumpt and F. Gomes, 1914)—Brazil—has a characteristic red band on the head, and lives in the burrows of *Kerodon rupestris* and those of armadillos. This species has been found infected with *Trypanosoma cruzi* at a considerable distance from human habitations.

P. dimidiatus (Erichson, 1848)—Brazil, Venezuela, British Guiana, and San Salvador—is also naturally infected with *T. cruzi* and possibly conveys the human disease in San Salvador.

P. geniculatus (Latrelle, 1811)—Paraguay, Brazil, Peru, Venezuela, and French Guiana—is a sombre-coloured species, living normally in armadillo burrows; it transmits *T. cruzi* to these animals.

Genus: *Triatoma*, Laporte, 1833.

Triatoma infestans (Klug, 1834)—South America—is a domestic species and lives in cracks in the walls of houses or hen-roosts. It is found naturally infected with *T. cruzi* in Argentina.

T. protracta (Uhler, 1894)—the United States, from Utah to California—is known as the "kissing bug," and lives in the burrows of rodents. Under natural conditions it harbours a trypanosome, *T. neotoma*.

T. rubrofasciata (de Geer, 1773), a cosmopolitan domestic species, can be infected experimentally with *T. cruzi*. It has been suspected, on rather imperfect evidence, of once transmitting kala-azar in India.

T. sanguisuga (Lecomte, 1855)—United States—is a common domestic species which associates with bed-bugs. Under experimental conditions it can be infected with *T. cruzi*.

T. sordida (Stal, 1859)—Brazil, Bolivia, and Paraguay—is a small domestic species met with near the banks of the large rivers; it has been found naturally infected with *T. cruzi*.

T. vitticeps (Stal, 1859)—Brazil—is the largest known of these insects, and is a rare species.

GENUS *Eratyrus* (Stal)

Eratyrus cuspidatus (Stal, 1859)—Venezuela—is rare, occurs at an altitude of 4,000 feet, and is naturally infected with *T. cruzi*.

GENUS *Rhodnius* (Stal, 1850)

This genus is characterized by a narrow attenuated head and by elongated antennæ (Fig. 445).

Rhodnius prolixus (Stal, 1859)—Venezuela, Colombia, Guiana, Brazil, and San Salvador. This species has nocturnal habits, and feeds voraciously on human blood. Normally it lives in the burrows of the armadillo and those of a rodent (*Catogenys subniger*).

The adult is capable of flying considerable distances; the larvæ and nymphs live in cracks in the walls and in the crevices of palm trees.

Under experimental conditions this species can transmit *T. cruzi*, and harbours *T. rangeli* (Pifano and Mayer, see p. 913).

A list of these bugs infected with *T. cruzi* and *T. rangeli* in S. America is given by Dias.

Rhodnius prolixus is the chief vector and *Triatoma infestans* in Brazil.

In Sao Paulo 25·19 per cent. infected.

In Minas Geraes 18·54.

In Rio Grande do Sol. 56·69.

In Paraíba *P. megrotus* and *Tr. maculata* are chief vectors.

Mexico—*Tr. sanguisuga*, *R. prolixus*.

Guatemala—*Tr. dimidiata*.

Panama—*Eratyrus cuspidatus*, *R. pallescens*.

Argentina—*R. prolixus*, *Eutriatoma sordida*, *T. infestans*.

Bolivia—*Eutriatoma sordida*, *T. infestans*.

Brazil—*P. megistus*, *Tr. brasiliensis*, *Eutriatoma sordida*, *Tr. chagasi*, *Tr. vitticeps*.

Chile—*Mapraia spinolai*, *Tr. infestans*.

Colombia—*R. prolixus*, *R. pictipes*.

Paraguay—*E. sordida*.

Uruguay—*E. sordida*, *Tr. infestans*.

Ecuador—*Eratyrus cuspidatus*.

Venezuela—*Eratyrus cuspidatus*, *Eutriatoma nigromaculata*, *P. rufotuberculatus*, *Psammolestes arthur* i, *P. geniculatus*, *R. prolixus*.

ORDER: SIPHONAPTERA (FLEAS)

Family: Acharopsyllidæ.

Fleas have laterally compressed bodies and are wingless, with mouth parts adapted for piercing and sucking blood. They are active ecto-parasites, almost exclusively of birds and mammals, and do not resist starvation. Many are moderately specific in their choice of host, but will migrate to another where necessary. The female is larger than the male, and in the former the curved *receptaculum seminis* forms a conspicuous feature. The eyes and antennæ are reduced, the latter fitting into a pit on the side of the head. The maxillæ are short and the mandibles function as cutting organs. Some have combs on the head and thorax. The body is contained in plates which represent a fusion of sternal, pleural and tergal portions. The ninth sternite is converted into a paired boomerang-shaped structure, and superficially looks like a clasper. White eggs are dropped by the female indiscriminately and hatch in summertime in three or four days. The larva lives in dust, feeds on debris, crumbs and faeces of adults, and is an active, footless maggot of a whitish colour, sparsely adorned with hairs (Fig. 446). When fully-grown, it spins a cocoon and pupates; the duration of this stage depends on temperature. A resting larval stage occurs, in which it can remain dormant for months. The pupæ are similar in shape to the adults,

and encased in a cocoon. The adult may remain thus encased as a resting adult stage or *hypopus*. Resting adults are probably aroused by vibrations in empty houses which have become re-inhabited. Inside the crop, or proventriculus, there is a patch of spines, about eight hundred in number, which help to crush up the red blood corpuscles of the host.

There are two main families:—*Pulicidae* (ordinary fleas), thirty genera, and *Tungidae* (chiggers), a small group.

Of *Pulicidae* five genera are important, and the following points are used for identification:—

1. Head and thorax without combs—*Pulex* or *Xenopsylla*.
2. Head, no comb; thorax with combs—*Nosopsyllus* (*Ceratophyllus*).
3. Head and thorax with comb—*Ctenocephalides* (*Ctenocephalus*).
4. Head pointed, without eyes—*Leptopsylla*.
5. Distinction between *pulex* and *xenopsylla* is based on the mesopleural plate:—

Pulex has no vertical bar: *Xenopsylla* has vertical bar.

Therefore, a flea without combs with vertical bar = *Xenopsylla*.

But a flea without combs, with antennal groove forming a thickening extending to top of head = *Pulex*.



Fig. 446.—Larva of *Xenopsylla cheopis*. Magnified.
(After Bacot and Ridgway, "Parasitology.")

Nosopsyllus fasciatus is the common rodent flea of temperate and tropical climates, and the dominant rat-flea of Europe. It will attack man in the absence of rats.

Ctenocephalides.—*C. canis* and *C. felis* are very similar and interchangeable between the dog and cat; they may also be found on rats. They attack man readily. (Fig. 447.)

Ctenopsyllus (*Leptopsyllus*) *segnis* is the mouse-flea and is also found on rats.

Hoplopsyllus anomalus infests ground squirrels and rats in the western U.S.A., has a pronotal comb, and plays a part in the dissemination of rodent plague.

Pulex irritans, the common human flea, has decreased in Europe enormously during the last thirty years but has penetrated many parts of the tropics; it is occasionally found on rats and pigs. (Fig. 449.)

Xenopsylla contains 30–40 species and is essentially an African genus; it requires a higher temperature to develop, and exists in heated buildings in England, America and Russia. (Fig. 448.)

X. astia (Rothschild, 1911).—In the male the antepygidial bristle is similar to that of *X. cheopis*, but it is easily differentiated by the shape of the ninth sternite, which, instead of being club-shaped, has the appearance of a ribbon, due to chitization of its ventral margin. The outer flap of the organs of copulation is narrower than in *X. cheopis*, and bears fewer bristles. The "tail" of the receptaculum is so strongly widened near the constriction that it is much wider than the head. The eighth segment has more than 30 bristles on the outer surface. (Fig. 451, 1.)

Xenopsylla brasiliensis (Baker, 1904).—In the male the long dorsal bristle on the seventh abdominal segment in front of the pygidium is placed on a long pedestal. In the female the "head" of the receptaculum seminis is very much wider than the "tail." (Fig. 451, 2.)

X. cheopis (Rothschild, 1903).—In the male the ante-pygidial bristle is situated on a short pedestal. The outer flap of the copulatory organs is sole-shaped; its upper edge is more curved than the lower, and bears 9 or 10 bristles on its outer surface, all of them thinner than in *X. brasiliensis*, and drawn out

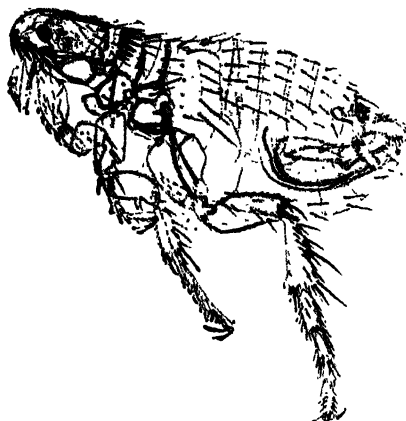
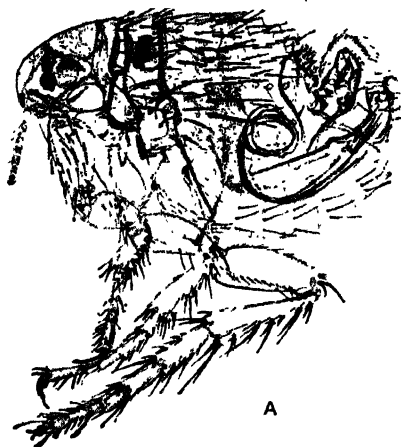


Fig. 447.—*Ctenocephalides canis*, male.
× 16.



Fig. 448.—*Xenopsylla cheopis*, male.
× 16.

(T. L. Bomford.)



A



Fig. 449.—*Pulex irritans*—A, male, × 25 ; B, female, × 14.
(T. L. Bomford.)



A



B

Fig. 450.—*Tunga penetrans* (*Dermatophyllus penetrans*, *Sarcopsylla penetrans*)—
A, female ; B, male. × 38. (T. L. Bomford.)

into a long, thin point. The ninth sternite has the appearance of a club, the upper side of which is flattened.

In the female the "tail" of the receptaculum is much longer than in the preceding species and, near the constriction, is distinctly wider than the "head." (Fig. 451, 3.)

X. cheopis must feed every ten days, except in the adult resting stage and in temperate climates. It may hibernate as an adult and so may remain infected with plague throughout the winter, as occurs in the case of rodent-flea plague in Siberia.

X. cheopis is widely disseminated on rats—*R. rattus*, *R. decumanus*.

X. brasiliensis on rats in Uganda, Kenya and Nigeria.

X. astia on rats in India, Ceylon, Burma and Iraq.

X. nubicus on rats in Tropical E. and W. Africa.

X. eridos on wild rodents in S. Africa.

Pulex irritans, universal in S. Africa on pigs and rodents.

Nosopsyllus fasciatus on *R. decumanus* in temperate zones.

Diamanus montanus on ground squirrels in W. U.S.A.

Rhopatopsyllus cavicola in S. American cavies.

Ceratophyllus tesquorum on ground squirrels on Russian steppes.

Oropsylla silantiewi on rodents in Manchuria.

Family: Tungidae.

Genus: *Tunga*.

Tunga penetrans (Jarocki, 1838), the "chigger flea" (see p. 673, Fig. 159 and Fig. 450), has a powerfully toothed mandible, a short thorax and slender legs. In the female the spiracles are massed at the hind end of the abdomen. In the early stages it behaves like other fleas, but when the female is impregnated, it attaches itself to the skin, especially of the feet, burrowing deeply with its mandibles until it becomes covered with skin with only the spiracles projecting. When filled with eggs the body swells enormously. When the eggs are discharged the female dies and sloughs away. The egg is oval, about 0.5 mm. in length. A larva emerges in three days, resembling other flea larvae, but has a chitinous structure on its head, the "egg breaker" with which it slits the egg-shell. Then it feeds on organic matter in dust and passes through two larval stages. A pupa is formed in 14 days. In the second stage the larva spins a silken cocoon within which it casts its skin and becomes pupa. The flea emerges in one week. *T. penetrans* originated in America, and has long been known in West and South Africa; but only comparatively recently in East Africa and West Coast of India.

Echidnophaga gallinacea: The Stick-Tight Flea—is a dangerous pest of poultry, but also attacks man occasionally, dogs, rabbits, cats, rats and horses. The adults are very active, but during copulation the female flea attaches herself to the skin and then burrows into it, forming a swelling which may ulcerate. In the lesion so produced the female lays eggs that drop to the ground, where the larvae develop as do other fleas.

Importance of fleas to man.—Flea bites may cause severe irritation in some individuals. This is largely an anaphylactic response in persons who are sensitized; subsequent desensitization may take place. Tapeworm eggs are eaten by fleas and encyst in the larva, pupa and adult, e.g., *Hymenolepis diminuta* of rat and *Dipylidium caninum* of dog. Endemic murine typhus is normally spread by fleas in the following rhythm:—

rat—rat louse—rat—rat flea—man.

Plague is essentially a disease of rodents spread by *X. cheopis* and other fleas by the method of "blockage" (see p. 259), which is due to their peculiar type of proventriculus. *X. astia* can transmit the plague bacillus, but is not nearly so effective as *X. cheopis*.

Identification.—Three species of *Xenopsylla*—*cheopis*, *astia* and *brasiliensis* are ectoparasites of the rat in India. It is not possible to make out the distinguishing features of the three species, unless the specimens are suitably prepared. With the aid of a hand lens, the females can be recognized by the shape of the spermatheca after the soft parts have been dissolved by caustic potash, or rendered transparent by means of a clearing agent. For the certain identification of the males, a compound microscope is necessary, when it can be seen that the ninth sternite ends in a sharp point in *astia*, instead of a flattened projection, as

in *cheopis*. The shape of the claspers differs in *astia*; they are more elongated. These differential characters can only be relied upon in fleas from the Indian area, because in that country only these three species exist.

After a short preliminary treatment with caustic potash, the fleas are treated with alcohol and xylol and placed overnight in a thin solution of balsam in xylol. Slides are prepared by coating the specimens with a thin layer of balsam and allowing them to dry overnight in the incubator. The fleas themselves are mounted and orientated on the slide; the insects can then be individually examined under the microscope in rows of five.

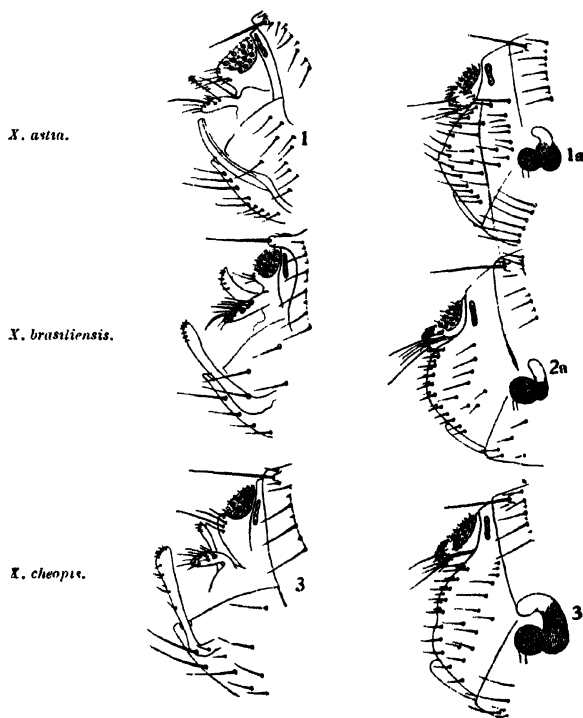


Fig. 451.—Diagnostic characters of *Xenopsylla* rat-fleas. Magnified.

(After Cragg and Hirst.)

1, *X. astia*: pygidium of ♂; 1a, pygidium and spermatheca of ♀; 2, *X. brasiliensis*: pygidium of ♂; 2a, pygidium and spermatheca of ♀; 3, *X. cheopis*: pygidium of ♂; 3a, pygidium and spermatheca of ♀. Note shape and size of spermatheca.

Prophylaxis.—To rid cats and dogs of these insects they should be washed with carbolic soap or a strong lather of “vermijelli.” Cats that object to water may be powdered with naphthaline or dusted with pyrethrum. The floors of the house should be washed with a solution of naphthaline or benzene. An emulsion of petroleum which will kill fleas when diluted with water, 1 in 20 or more, may be made from soft soap and ordinary petroleum, 3 parts of soap being melted by heat in 15 of water, and 70–100 parts of oil added while still

hot, with much shaking and stirring. The final mixture should be white and creamy. For destruction of fleas by DDT, *see* p. 860.

The irritation of flea-bites may be allayed by the application of 1 in 20 carbolic. The best repellents for fleas are dimethyl phthalate, Rutgers 612 and indalone.

Rat flea survey.—This consists of collecting information on an abundance of fleas and identifying the species at different seasons. Single rats should be caught alive and kept under observation. Fleas should be collected, counted and examined. Rats must be kept apart, for if two are together they will fight and interchange fleas. The rats are killed so as to preserve all their fleas. The trap should be put into a white bag in a chamber filled with cyanide gas, which kills rat and fleas together. The fleas should be mounted in pure carbolic. Record should be kept of the species and sex of the rat, the species and numbers of fleas present.

Flea-index = number of fleas per rat, and is used in making surveys of plague.

SECTION B.—CLINICAL PATHOLOGY

I.—CLEANING SLIDES

New slides are suitable for making blood-films, but only when superficial grease has been removed by breathing on them and rubbing briskly with a clean handkerchief.

Slides which are dirty or have previously been used should be boiled in soapy solution for about half an hour, then washed in several changes of water, dipped in methylated spirit, and polished with an old linen cloth.

Cover-slips and slides are apt to become frosted when kept for long in the tropics; in order to prevent this they should be stored in spirit.

II.—CARE OF MICROSCOPES AND GLASS WARE

In the tropics, especially where the wet-bulb temperatures are high, fungi are apt to overgrow the lenses of optical instruments. They may even etch or stain the glass and ruin the lenses. Of the fungicides, sodium ethylmercurithio-salicylate is most effective when incorporated in concentration of 0.2 per cent. in a black lacquer which is used for coating the interior metal surfaces of optical instruments. The aim of the manufacturers has been to improve the sealing of instruments and by employing a desiccant to render the use of fungicides unnecessary.

The microscope, when not in use, should be protected by a cellulose acetate hood, similar to those used in biological laboratories. The hood is made sufficiently high to include a microscope supported by a small wooden table, under which is placed a container with calcium chloride to maintain dryness. The edges of the hood are made air-tight by cementing with acetone. The cylindrical shape of the hood is achieved by attaching three wire hoops to the inside with adhesive tape. The hood stands in a wooden box having a circular groove $\frac{1}{4}$ in. wide and $\frac{1}{4}$ in. deep, containing metallic mercury, which forms an

air-tight joint, but is not sticky, like petroleum jelly (Fig. 452). This can be supplemented by rings of soft rubber hose tacked on to each edge of the groove and which makes a closely fitting additional joint into which the hood may be slipped (White, 1946).

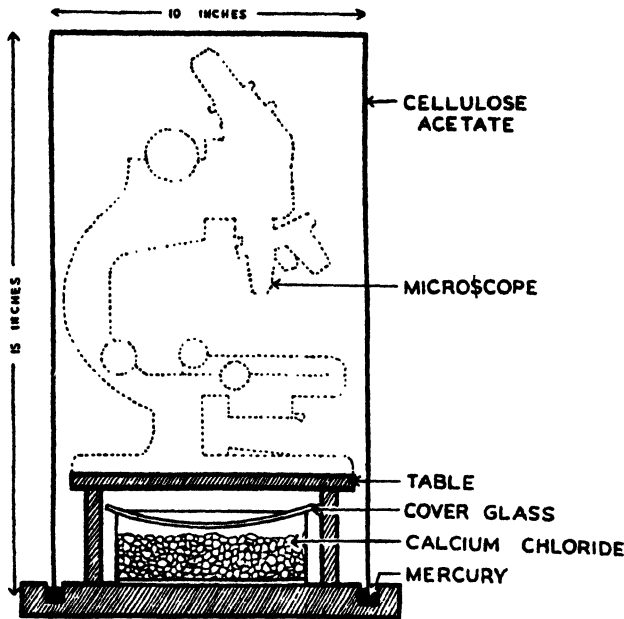


Fig. 452.—Cellulose acetate hood for protecting precision instruments in the tropics. (Courtesy of *Tropical Agriculture*.)

III.—METHODS OF PREPARATION OF BLOOD-FILMS

THIN FILMS

A drop of blood, obtained by pricking the cleansed finger or ear-lobe,¹ is taken on to the end of a glass slide, without exerting any undue pressure, and avoiding contact with the skin. The drop thus obtained is impinged upon a second slide

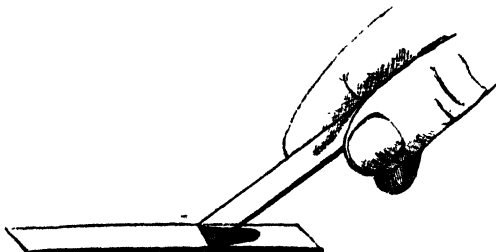


Fig. 453.—Method of spreading a blood-film.

about $\frac{1}{4}$ in. from the end, and the blood permitted to spread evenly. The spreading slide should be pushed, at an angle of 45° , to the opposite end of the horizontal,

Blood from the ear is not so satisfactory as that obtained from the finger.

leaving a thin and evenly-spread film which should then be allowed to dry. (Fig. 453.) An angle of less than 45° makes a thin, and one greater than this a thicker, film. (Figs. 454, 455.)

A lancet-pointed hare-lip pin is a satisfactory instrument for pricking the finger.

Films for differential cell count should be prepared by pressing unevenly upon the slide so as to obtain a wave-like film. By this method the leucocytes congregate at the edges of the waves, thus facilitating enumeration.

THICK FILMS

Ross's thick film is best made by the aggregation of six drops of blood on a slide within an area 5-7 mm. in diameter, which is then spread into an even layer. After dehaemoglobinization with water, the resulting film is dried in air. It should then be stained with Leishman's or Giemsa's stain, as detailed.

Distortion of blood protozoa and leucocytes in such a film can be obviated by use of stains in isotonic solution. The stain should be buffered to pH 6.6 to 7.0. Retention of some of the haemoglobin is advantageous as it provides a pale yellow contrast background.

Field's thick film.—The blood-drop should be about the size of a sixpence and thin enough to see the hands of a watch through it. The films should be dried and stained when fresh.

Two solutions are necessary, both isotonic and adjusted to pH 6.6 :—

<i>Solution 1</i>		<i>Solution 2</i>	
Methylene blue	0.8 grm.	Eosin	1 grm
Azure B	0.5 grm.	Disodium hydrogen phosphate (anhydrous) ..	5 grm
Disodium hydrogen phosphate (anhydrous) ..	5.0 grm.	Potassium dihydrogen phosphate (anhydrous) ..	6.25 grm
Potassium dihydrogen phosphate (anhydrous) ..	6.25 grm.	Distilled water	500 ml
Distilled water	500 ml.		

The dye solutions are stood for twenty-four hours and filtered. Staining is performed by dipping the film for one second in solution 1, rinsing in water till the stain ceases to flow, then dipping for a similar period in solution 2, rinsing in clear water and placing in a vertical position to dry.

There is some difficulty in differentiating younger forms of tertian and quartan from subtertian malaria parasites by these methods, such details as Schüffner's dots being usually invisible (*see Microscopic Diagnosis of Human Malaria* 1. Field, J. W. (1948). Studies from the *Inst. Med. Res., Federation of Malaya*). They are, however, very useful for demonstrating parasites in scanty infections, especially rings and gametocytes, and also spirochaetes of relapsing fever and trypanosomes when these, as so often, are scanty (*see Plate III, 2, p. 71*).

Films for demonstration of filarial embryos.—An even larger-sized drop should be taken (20 c.mm.) and spread so as to occupy an area of $\frac{1}{4}$ sq. in. (Fig. 455.) For this purpose the finger should be pricked with a broad-pointed needle and the surface of the slide dabbed with four good-sized drops. The film is allowed to dry, protected from dust (especially from cotton fibres, which may simulate microfilariae), dehaemoglobinized with water, and stained in a dilute watery solution of fuchsin (5 drops to 150 ml. distilled water), then examined wet under a low power of the microscope.

SKIN SCARIFICATION

Van den Berghe and Chardome (1951) describe an easier and more accurate method of diagnosis of malaria and filariasis by skin scarification smears.

A site is superficially cut so that little bleeding takes place. Finally the scarified area is squeezed between the thumb and forefingers. The dermal capillary blood then obtained is spread either as a thick or thin film on a slide, is stained and examined in the usual way. The microfilariae of *Mansonella ozzardi*, *D. perstans*, *D. streptocerca*, *W. bancrofti*, *W. malayi*, *L. loa* and *O. volvulus* are readily found. It is claimed also that a higher percentage of malaria infections is revealed by this method than by examination of thick films.

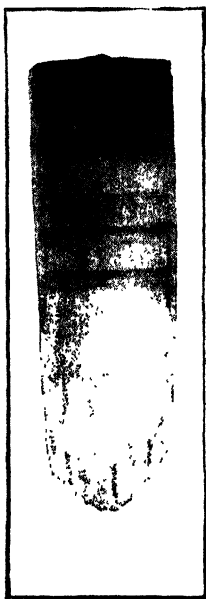


Fig. 454.—Successful thin blood-film.

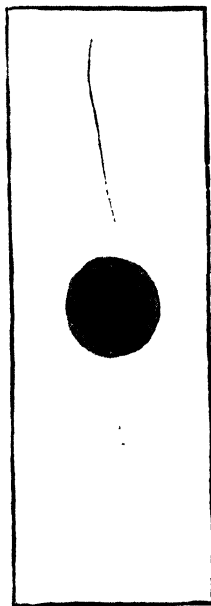


Fig. 455.—Thick blood-film.

PREPARATIONS FOR THE STUDY OF FRESH BLOOD

A small drop of blood should be taken upon a clean slide, inverted, and allowed to come into contact with a clean cover-slip upon filter-paper. If no pressure is used, the blood spreads out evenly, the corpuscles tending to congregate round the periphery while the centre remains clear. The preparation may then be ringed with vaseline, and the blood-cells or contained parasites studied under a $\frac{1}{2}$ -in. lens. For living cells (vital staining), a vaseline ring or square of the size of a cover-slip is made upon a clean slide. Then a solution of 0.85 per cent. NaCl with 1 per cent. sodium citrate tinted with methylene-azur, gentian-violet or methyl-green, is taken up in a capillary pipette, together with an equal volume of blood. After mixing, a small drop is placed in the centre of the vaseline ring and immediately covered with the coverslip and pressed down.

IV.—STAINING BLOOD-FILMS FOR BLOOD, INTESTINAL PROTOZOA AND DIFFERENTIAL COUNT OF CELLS

Leishman's method.—For this method *no preliminary fixation* is required.

Preparation of stain from the powder is made with 0.15 per cent. solution of methyl alcohol (acetone-free). In the tropics amyl alcohol is preferable, as it does not evaporate so readily. The powder is placed in a glass mortar, a quantity of methyl-alcohol added, and then ground down with a pestle until the alcohol is saturated. The fluid is decanted off into a clean bottle and a further fraction of methyl-alcohol added to the residue in the mortar, which is again ground down until as much as possible is dissolved. This process is repeated until the whole of the powder is in solution, and sufficient methyl-alcohol is finally added to make up the required volume.

Staining.—1. Select the most suitable part of the blood-film and place a grease-pencil mark on each side, about 1 in. apart—a method which, in staining large batches, results in great economy. 2. Cover the selected part with stain by means of a pipette, and leave for a minute, taking care that it does not dry. 3. Dilute the stain 1 in 4 with distilled water, *which must not be acid in reaction* (fresh rain-water may be used), and allow to act for a further 5 mins. 4. Wash off the stain with distilled water and leave a drop on *for a minute* to differentiate; then place in a sloping position to drain.

For permanent preparations, Leishman-stained slides must *not* be mounted in Canada balsam, as they rapidly fade, unless it is neutral in reaction or dammar lac be used; they should be examined, unmounted, direct in cedarwood oil, which can be subsequently removed by xylol.

Giemsa's stain.—It is best to obtain the stain already prepared for use by Grüber. *The film must first be fixed* in a mixture of equal parts of absolute alcohol and ether for 10–15 mins.

Staining.—1. The film should be covered with a 1 in 20 dilution of the stain (1 drop to 19 drops distilled water (1 ml. of stain to 15 ml. distilled water), which is allowed to act for 20–30 mins. 2. Wash off the stain with distilled water. Place the slide in a sloping position to drain, or dry with blotting-paper.

Shute's modification.—Normal saline (0.85 sodium chloride), buffered to pH 7.4, is used instead of distilled water. The films are stained for 30 minutes. Staining is greatly improved. The background is clear because the envelopes of all uninfected cells have been removed. The parasitized cells remain, and in *P. vivax* infections, Schüffner's dots stand out. Films can be stained in bulk.

Hæmatoxylin and eosin.—This method is employed for studying the finer structure of leucocytes, and especially nuclear changes.

After fixation in alcohol and ether for 10 mins. the film should be stained with Delafield's hæmatoxylin for 7 mins. It should be well flushed off with a

Fig. 456. — McKay's method of staining flagellated body.

1, Slide bearing freshly-made blood-film; 2, pad of damp filter-paper; 3, size of opening showing blood-film and forming with the opposing slide an hermetically sealed damp chamber.

good flow of tap-water, and left in a running stream for an equal period in order to "blue." While still wet it should be counterstained with a watery solution (5 per cent.) of eosin for 30 secs., after which it should be thoroughly rinsed in tap-water for another 3 mins. to differentiate.

Methods of staining the flagellated body in malaria.—A sheet of thick blotting-paper, fenestrated with rows of oblong holes (1 in. by $\frac{3}{4}$ in.), is prepared. It is then moistened with water, and laid smoothly on a sheet of window-glass.

A patient in whose blood the crescent form of the parasite abounds is selected. A clean microscope slide is breathed upon, and the droplet of gametocyte-containing blood taken up by lightly touching it with the centre of the moistened slide. The blood is now rapidly, and somewhat unevenly, spread out with a needle so as to cover an area of about $\frac{3}{4}$ in. by $\frac{1}{2}$ in. The slide is immediately inverted over one of the blotting-paper cells and pressed down sufficiently to secure thorough apposition of the slip without bringing the blood into contact, either with the moistened paper forming the wall, or with the glass forming the floor of what is now a perfect moist chamber. The remaining paper cells are rapidly covered with blood-charged slides prepared in the same way. They are removed and dried at intervals of from 5–20 mins. and subsequently stained by Leishman's method.

McKay's method.—This is an abbreviated, but more effective method. A thin film of crescent-containing blood is made upon a thin slide (1 mm. in thickness, so as to be easily focused through a $\frac{1}{4}$ -in. lens). The wet film should be breathed upon and then placed face downwards upon a second slide covered with a small piece of damp filter-paper with a small central opening. The two slides are bound together by elastic bands, thus forming a tightly sealed damp chamber. Exflagellation of the crescent can now be observed under the microscope, and immediately this occurs the film is dried and stained. (Fig. 456.)

Kohn's one-stage permanent staining method for Fæcal Protozoa, especially for *Entameba histolytica*, *E. coli* and *Giardia*.

90 per cent. Ethyl alcohol	170 ml.	} Basic solution.
Methyl alcohol	160 ml.	
1 per cent. Phosphotungstic acid	12 ml.	
Glacial acetic acid	20 ml.	
Liquid phenol	20 ml.	
Distilled water	up to 1 litre	
Chlorazol black (G. T. Gurr)	5 grm.	

The chlorazol black must be ground finely in the basic solution until all is dissolved and then ripened for two weeks. The clear supernatant fluid is used for staining. Smears made on coverslips are placed surface downwards and left overnight. The process can be speeded up by placing in incubator for 3–4 hours. If the material is very fluid prepared coverslips should be placed in Bouin's fluid. For sections the stain is diluted twice with distilled water. Differential staining is obtained. In *E. histolytica* ingested red corpuscles are picked out a bright red, *E. coli* cysts are stained pink.

V.—VARIETIES OF BLOOD-CELLS AND THEIR SIGNIFICANCE

(Plate XXVI)

The average total leucocyte-count, made by a Thoma-Zeiss hæmocytometer, is 7,000 per c.mm. of blood. A rise to above 10,000 indicates *leucocytosis*, a fall to below 5,000 *leucopenia*. In a differential leucocyte-count, at least 300 cells should be counted under the $\frac{1}{4}$ -in. immersion lens, and by means of a movable

stage the preparation should be moved from side to side, so as not to traverse the same field twice.

Myelocytes are produced by division from myeloblasts and are smaller than the parent cell. The nucleus is oval or kidney-shaped with characteristic granules in the cytoplasm and can be divided into neutrophil, eosinophil and basophil cells, according to the colour of their granules. The more mature cells are capable of showing amoeboid movement. These cells are rarely found in the blood stream, but can pass through the spaces between the intact endothelial lining of the sinusoid walls, as do other granulocytes. Three stages of maturity are known as *premyelocytes*, *myelocytes* and *metamyelocytes*. The neutrophil myelocyte normally predominates in the marrow.

Neutrophil polymorphonuclear (or microphage) ($12\ \mu$).—Normal proportion, 35–70 per cent.; average, 67. With Romanowsky stains, neutrophil granules usually stain slightly acidophil. Variation in shape of nuclei is due to subdivision of the nucleus from one to four or even more lobes, affording some indication of the age of the cell. Thus, a count of these cells according to the numbers of lobes is an aid to diagnosis known as the “Arneth index.” A shift to the left is found in liver abscess, pneumonia, relapsing fever, or, indeed, in any septic process. (Pl. XXVI, 1.)

Increased in acute pyogenic infections, actinomycosis, leptospirosis, cholera, oroya fever, smallpox, scarlet fever, typhus, amoebic hepatitis, amoebic abscess of liver, rheumatic fever, acute rheumatoid arthritis, periarteritis nodosa, myeloid leukaemia, diabetic and uraemic comas. *Agranulocytosis* (sometimes called *neutropenia*) is a severe depression or absence of granulocytes usually associated with anaemia. Most commonly found with drugs—sulphonamides, thiouracil, amidopyridine, gold, arsenic and benzene, and also in kala-azar.

The precursor of the polymorphonuclear is a bone-marrow cell, the *myelocyte*, of which mature individuals contain granules and mitochondria.

Eosinophil ($12\text{--}14\ \mu$).—Little larger than the polymorphonuclear, these cells contain coarse eosinophil granules. Usually, the nucleus has not as many lobes as the polymorphonuclear, two being about the average number (“spectacle arrangement”). The normal proportion is 2–4 per cent.; average 3 per cent. Eosinophils are increased in most helminthic diseases—in ancylostome, dracunculosis, and clonorchis infections, 5–10 per cent.; in filariasis and paragonimiasis, 10–20 per cent. (*L. loa* infections possibly 60 per cent.); in schistosomiasis and trichiniasis, 20–60 per cent. of the total leucocyte-count. On the other hand, in ascariis and diphyllbothrium infections there may be no appreciable increase. (Pl. XXVI, 5). The greatest increase is in Tropical Eosinophilia (see p. 686) and in Löffler's Syndrome in trichiniasis, asthma, urticaria, in skin diseases—dermatitis, pemphigus, eosinophilic leukaemia, scarlet fever, congenital familial eosinophilia, Addison's disease, periarteritis and after cortisone therapy.

Basophile ($10\text{--}12\ \mu$).—This is slightly smaller than the polymorphonuclear. The nucleus is kidney-shaped, or slightly lobulated. The cytoplasm contains large purple granules which often obscure details of the nucleus. Usual proportion is 0.5 per cent. (Pl. XXVI, 6), except in chronic myeloid leukaemia.

Lymphocyte.—This is derived from the lymph-glands and other collections of lymphatic tissue. The *lymphoblast* contains an oval nucleus, poor in chromatin, with a reticular structure, coarser and more stippled than the myeloblast, and is found in acute lymphatic leukaemia. The normal proportion is 19–30 per cent.; average, 23. The small lymphocyte is 5–8 μ ; the large 12–15 μ , though the latter is assumed to be the immature form. This cell is normally increased after physiological digestion, in undulant fevers, pellagra, typhoid, pertussis,

lymphocytic, leukæmia, glandular fever (with abnormal forms), rubella, chronic tuberculosis, and relatively in kala-azar. (Pl. XXVI, 2, 3.)

Large hyaline, or mononuclear (monocyte-macrophage, and transitional). (16–22 μ).—Normal proportion, 3–8 per cent.; average, 6 per cent. This cell is increased in protozoal diseases—amœbiasis, trypanosomiasis and malaria; in the latter it often contains ingested hæmozoïn. Should the ear be selected for obtaining blood, it is important that no drop earlier than the third should be used, for it has been shown that these cells tend to accumulate in the capillaries of the ear, if the local circulation is slow. It is now understood that large mononuclears are derived from the spleen and bone-marrow and are not related to the lymphocyte. Therefore “transitional cells” must be regarded as mature mononuclears. The cytoplasm contains fine reddish-blue granules. (Pl. XXVI, 4.)

The *monocyte* has to be distinguished from the *class. atocyte*. The former originates from the reticulum: the latter from the endothelium. They both have the same morphology, staining reactions, and nuclear structure, as shown by ordinary stains, but in vital staining, the clasmatocytes take up trypan-blue, while monocytes do not.

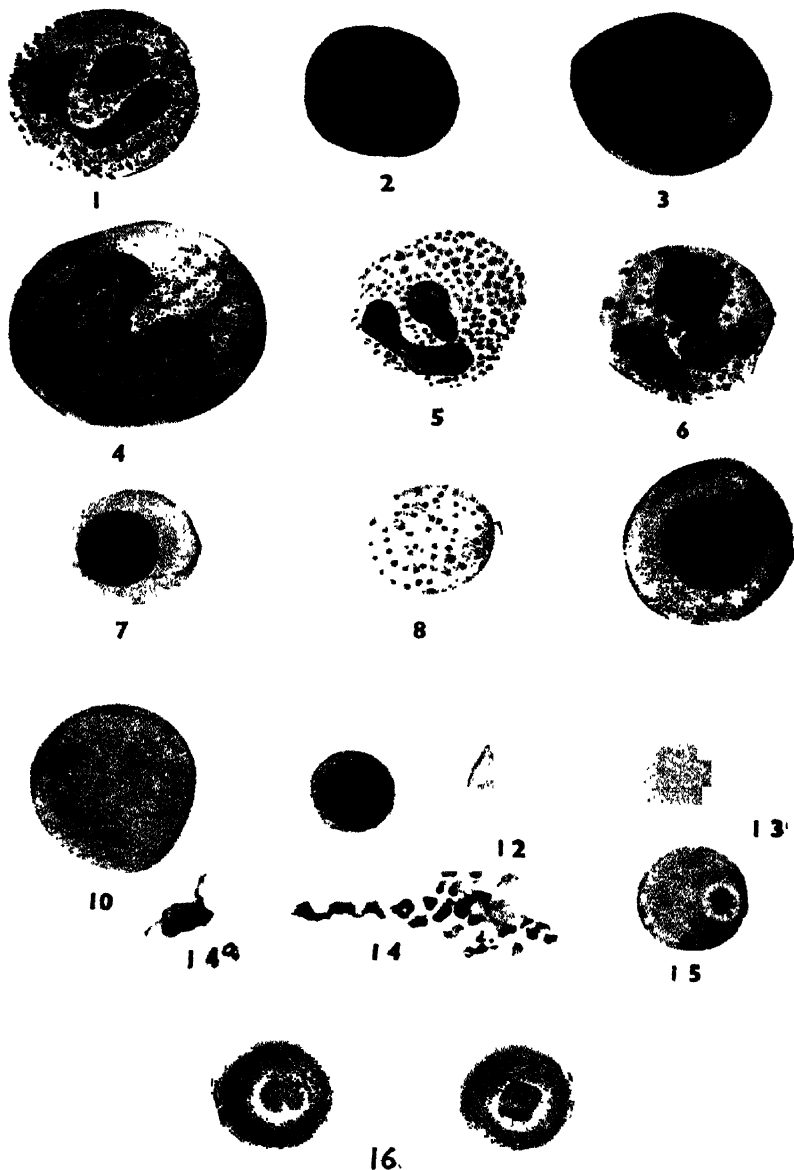
A proportion of 15 per cent. or more of these cells may be considered a reliable aid to the diagnosis of malaria; 10 per cent. may occur in a normal person, and any increase above this calls for further investigation. There is an increase of monocytes during the pyrexia of a primary malarial attack, but a lymphocytosis is associated with relapse. The number is increased in monocytic leukæmia, typhoid, typhus, glandular fever, Hodgkins disease, and tetrachlorethane poisoning.

Leucocytes in childhood.—These are more numerous than in the adult; 12,000 per c.mm. is the average number throughout infancy. The percentage of lymphocytes is doubled, that of the neutrophils is halved. The adult proportion is reached about the tenth year.

Normal red cell (erythrocyte). (7.2–7.5 μ).—Normal number, 5,000,000 per c.mm., or more. They are biconcave discs, and therefore thinner in the centre than at the periphery. Erythrocytes are derived from reticulocytes in the bone marrow. The cell membrane of the latter is sticky, so that the cells adhere to one another and to the capillary wall. In the process of maturation this property gradually diminishes. Abnormal red cells are known as ovalocytes, and elongated forms as sickle-cells (p. 23). A total red count, computed from 64 squares on the Thoma-Zeiss hæmocytometer, of under 3,000,000 denotes severe anæmia, and is usually accompanied by changes in the red cells—e.g., in malaria, blackwater fever, tropical sprue, ancylostomiasis and Oroya fever.

Distinctive forms of red cell, *reticulocytes*, are young red cells formed from normoblasts by fragmentation of the nucleus. They constitute a constant sign of blood-regeneration, and are supravitaly stained by cresyl-blue. They are larger and stain more lightly than mature red cells and their stroma contains a blue-staining reticulum. In normal blood these cells amount to 1 per cent., 4 per cent. in infants, but during blood-regeneration they may reach 20 per cent. or more and are found in pernicious and hæmolytic anæmias, after splenectomy and in lead poisoning.

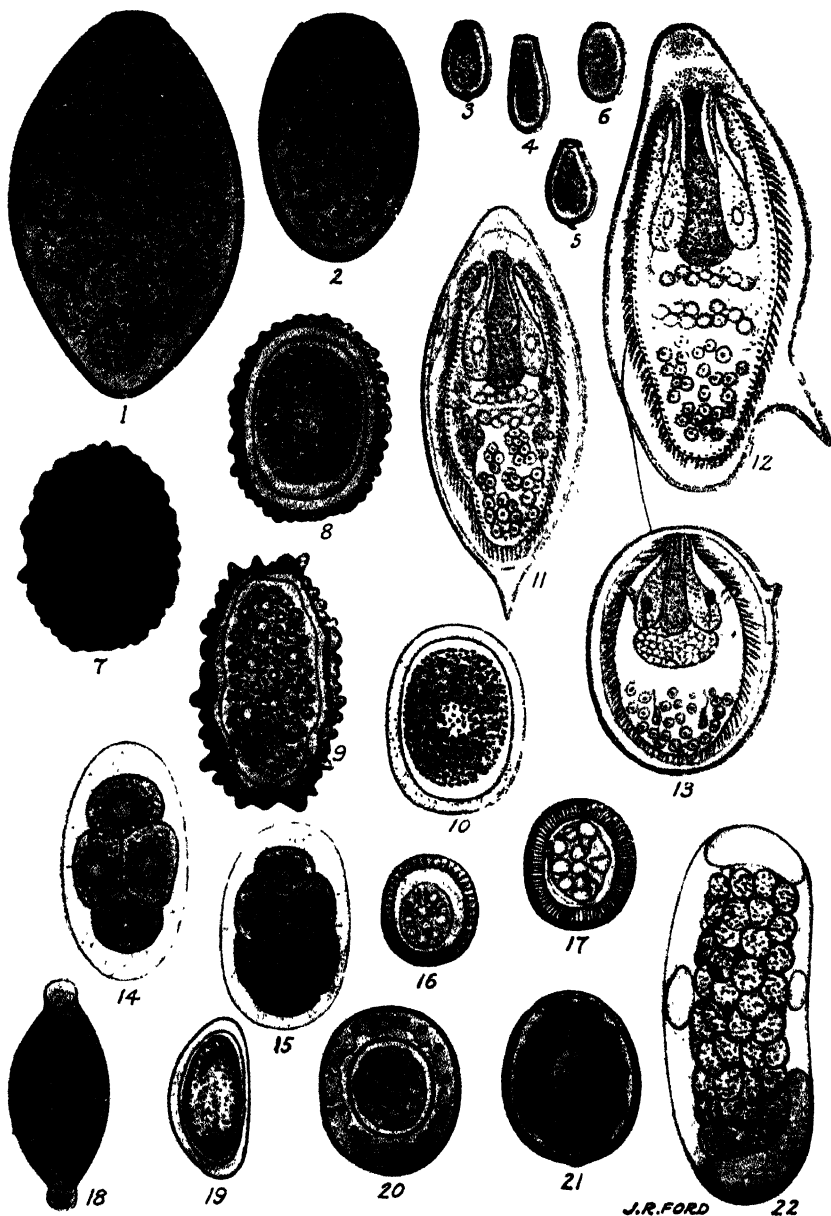
Anisocytosis denotes variations in size of red cells; it is found in various conditions of anæmia, especially of the pernicious type. **Poikilocytosis** (Pl. XXVI, 12) denotes pear-shaped distortion of cells, giving the idea of fragmented corpuscles, and is found in anæmic conditions.



NORMAL AND ABNORMAL BLOOD CELLS

x 2,000 (Leishman's stain)

PLATE XXVI



**EGGS OF THE COMMONER HELMINTHS
FOUND IN MAN**

Megalocytes (Pl. XXVI, 10).—These are red cells of increased size, 7.2-7.5 to μ in diameter, and abnormal shape, generally associated with microcytes (Pl. XXVI, 11) which are red cells smaller than the normal. Megalocytes occur in the blood in the severe anæmias of blackwater fever, subtertian malaria, Oroya fever, tropical sprue, and pernicious anæmia.

Normoblasts.—Are seen in small numbers in normal blood, and are increased in severe anæmias. Nucleated red cells may be seen in carcinoma, miliary tuberculosis, pernicious anæmia, leukæmias, malarial cachexia, blackwater fever, tropical sprue, ancylostomiasis, kala-azar, and Oroya fever, in severe helminthiasis, and in newborn infants, especially with erythroblastosis fœtalis. The nucleus is sometimes double or bilobed, and the protoplasm of the cell is usually polychromatophilic. Supravital staining shows a well-marked reticulum in the cytoplasm. These cells are generally present in considerable numbers in spleen and bone marrow punctures in kala-azar, severe malaria, visceral schistosomiasis, pernicious and splenic anæmias. (Pl. XXVI, 7.)

Sickle cells.—In sickle-cell anæmia and in sickle-cell trait (may only appear at low particle pressure of oxygen (*see* p. 24).

Oval cells (Elliptocytosis) in Thalassæmia (Cooley's anæmia, *see* p. 29).

Spherocytes in congenital spherocytosis (Familial acholuric jaundice), in which there is an increase in thickness of the red cell.

Polychromatic degeneration of red cells (Pl. XXVI, 13).—This is a phenomenon found in subtertian malaria, blackwater fever, and severe anæmia. The term *polychromasia* denotes degeneration of the red cell, the cytoplasm of which stains light blue; when severe it is generally accompanied by the formation of polychromatic, or basophilic, dots (Pl. XXVI, 8). It is now generally accepted that *polychromasia* and stippling are both manifestations of reticulation, so that polychromatic cells in a Leishman-stained film and reticulocytes of a supravital-stained film are considered identical. Polychromasia is found in malaria, Oroya fever, pernicious anæmia, ancylostomiasis, and lead-poisoning. In thick films the depth of colour of the blue background has been found to afford some indication of the extent of reticulocytosis.

Target Cells or *Leptocytes* (Pl. XXVI, 16) are normocytes with coloured centres and borders, separated by a pale ring which gives them a "mexican hat" or target-like appearance. The term *leptocyte* refers to their thinness. The presence of large numbers of these cells in the blood is pathognomonic of Cooley's anæmia (or Thalassæmia), but they occur fairly often in diverse other types of anæmia, hæmoglobin C and E diseases. Isolated target cells are also seen in the blood of normal people.

Megaloblasts.—These are abnormal nucleated red cells found in severe anæmias of the pernicious type, including some diphyllbothrium infections; their size is sometimes twice that of a normal erythrocyte. The cytoplasm is non-granular and deeply basophilic, the nucleus large and pale, occupying more than half the cell body, which contains no hæmoglobin. (Pl. XXVI, 9.)

Howell Joly bodies.—These are small blue chromatic dots in the centre of the erythrocyte, and denote nuclear remains. Occur after splenectomy, occasionally in virus pneumonia and are liable to be confused with malaria parasites.

Cabot's rings.—A central circular ring is frequently seen in erythrocytes in anæmic blood, and considered to represent part of the nuclear envelope.

Demilunes (Sergeant).—These are intracorpuseular vacuoles.

Blood-platelets (3μ in diameter) (Pl. XXVI, 14, 14a).—These are round, oval, or rod-shaped, according to the viewpoint, but variability in size is a feature of essential thrombocytopenia. When resting on red cells they may simulate

PLATE XXVI

NORMAL AND ABNORMAL BLOOD-CELLS

- 1.—*Neutrophile polymorphonuclear leucocyte.*
- 2.—*Small lymphocyte.*
- 3.—*Large lymphocyte.*
- 4.—*Hyaline or large mononuclear leucocyte.*
- 5.—*Eosinophile leucocyte.*
- 6.—*Basophile leucocyte ("mast cell").*
- 7.—*Normoblast (nucleated red cell).*
- 8.—*Basophilic dots in red cell.*
- 9.—*Megaloblast.*
- 10.—*Megalocyte.*
- 11.—*Microblast.*
- 12.—*Microcyte showing poikilocytosis.*
- 13.—*Polychromatophilic degeneration of red cell.*
- 14, 14a.—*Various appearances of blood-platelets.*
- 15.—*Blood platelet superimposed upon a red cell.*
- 16.—*Target cell, or "Mexican hat," red cells, found in sickle-cell anæmia and Thalassæmia.*

PLATE XXVII

EGGS OF THE COMMONER HELMINTHS
FOUND IN MAN. × 400.

- 1.—*Fasciolopsis buski*.
- 2.—*Paragonimus ringeri*.
- 3.—*Heterophyes heterophyes*.
- 4.—*Opisthorchis felineus*.
- 5.—*Clonorchis sinensis*.
- 6.—*Metagonimus yokogawai*.
- 7.—*Ascaris lumbricoides* (external aspect).
- 8.— " " "
- 9.— " " (unfertilized egg).
- 10.— " " (decorticated egg).
- 11.—*Schistosoma hæmatobium*.
- 12.— " *mansoni*.
- 13.— " *japonicum*.
- 14.—*Ancylostoma duodenale*.
- 15.—*Trichostrongylus colubriiformis*.
- 16.—*Tænia solium*.
- 17.— " *saginata*.
- 18.—*Trichuris trichiura*.
- 19.—*Enterobius vermicularis*.
- 20.—*Hymenolepis nana*.
- 21.—*Diphyllbothrium latum*.
- 22.—*Heterodera radiculicola* (non-parasitic, ingested with vegetables).

malaria parasites, but there is always a clear zone due to surrounding pressure (Plate XXVI, 15). When drawn out in making the film they may simulate a trypanosome. They are generally found in masses or in strings, are coated with adhesive substance, and cling to any stationary object. Their function is connected with blood clotting.

VI.—MICROSCOPICAL EXAMINATION OF THE FÆCES AND FOR EGGS OF INTESTINAL PARASITES

The eggs of tapeworms, with the exception of *Diphyllobothrium latum*, and threadworm (*Enterobius vermicularis*) (Plate XXVII, 19) are rarely found in the stools, as these parasites do not, as a rule, part with their eggs until the segments of the former, or the entire body of the latter, have left the alimentary canal. Occasionally, the eggs of hepatic and intestinal parasites, such as *Schistosoma hæmatobium*, *S. mansoni*, *S. japonicum* (Plate XXVII, 11, 12, 13), *Clonorchis sinensis* (Plate XXVII, 5), *Fasciola hepatica*, *Fasciolopsis buski* (Plate XXVII, 1), *Heterophyes heterophyes* (Plate XXVII, 3), and of rarer helminths, are encountered.

The microscopical examination of fæces for eggs is by no means difficult. Place on the slide a minute portion of the suspected fæces, the size of a hempseed, and apply the cover-glass, gently gliding it over the slide so as to spread out the mass in a thin, fairly uniform and transparent layer.

The points to be attended to in the identification of eggs are size, shape, colour, thickness, roughness, smoothness, and markings on the surface of the shell; the presence or absence of yolk spheres, of a differentiated embryo, or, in the cestodes, of the three pairs of embryonic hooklets; the existence of an operculum in certain trematodes and in the broad tapeworms (*Diphyllobothrium*). Eggs of the same species of parasite vary slightly, but are in every instance sufficiently stable and definite for correct diagnosis.

Of the three common nematodes—*Trichuris trichiura* (Plate XXVII, 18), *Ascaris lumbricoides* (Plate XXVII, 7) and *Ancylostoma duodenale* (Plate XXVII, 14)—the eggs of the first are the most frequently met. Those of *T. trichiura* occur sometimes in enormous numbers, as many as six or eight specimens being visible in one field of an inch-objective. They form rather striking objects under the microscope. They are oval, measuring 51 to 54 μ by 22 μ , the ends of the long axis of the oval being slightly pointed, and tipped with a little shining projection or plug. Their general appearance suggests an elongated oval tray, the projections at the poles of the ovum representing the handles. They are dark brown, sharply defined, doubly outlined, and contain no differentiated embryo.

Eggs of *Ascaris lumbricoides* are considerably larger (50 to 75 μ by 40 to 50 μ) than those of trichuris. As a rule they are more spherical or, rather, more broadly oval; occasionally they are almost barrel-shaped. Like those of trichuris, they are dark brown from bile-staining, but they are much less sharply and smoothly defined, possessing a coarse thick shell, which is roughened by many warty excrescences. The yolk contents are not always easily made out, nor, when made out, can any indications of embryo or segmentation be discovered. In certain instances the eggs are smooth on the surface, the rough outer layer being almost or altogether absent. In this condition they are unfertilized.

A point of practical importance is that the rough outer layer of the shell of the egg of ascaris is very easily detached, leaving it with a sharp, smooth outline suggesting some other species of parasite. To obviate this, in mounting fæces it is well to avoid too much gliding of the cover-glass over the slide.

Eggs of *Ancylostoma duodenale* contrast very markedly with both the foregoing, particularly in colour. Trichuris and ascaris eggs are invariably dark and bile-

stained ; those of the ancylostome are beautifully clear and transparent, measure 55–60 μ by 32–40 μ , and have a regular, somewhat elongated oval form, with a delicate, smooth, transparent shell, through which two, or four, or eight light-grey yolk segments can be distinctly seen. Eggs should be looked for soon after the fæces have been passed ; otherwise, owing to the rapidity with which, in favourable circumstances, development proceeds, the embryo may have quitted the shell and the egg be no longer visible. The eggs of *Necator americanus* cannot be differentiated from those of *A. duodenale* with certainty. The eggs of *Trichostrongylus colubriformis* also resemble those of *A. duodenale*, but they are relatively larger and contain a fully segmented morula (Plate XXVII, 15).

The eggs of *Heterodera radicola*, or *H. marioni*, which have a characteristic appearance (Plate XXVII, 22), have been noted from time to time in the fæces of otherwise normal individuals since their discovery by Kofoid and White in 1919. *H. radicola* is a common root-parasitic nematode living in a variety of plants, such as radishes, celery, carrots and turnips; it is therefore apt to be encountered in the excreta of individuals who have ingested these vegetables. Of conspicuous asymmetric appearance and size, 95 μ by 40 μ , it might well be regarded in human fæces as an indication of nematode infection of the intestinal canal. A feature of the egg is the presence of two highly refractile, flattened, bluish-green globules at the poles of the embryo. As a rule they are kidney-shaped, and can pass uninjured through the alimentary canal.

The eggs of the cestodes may be distinguished from those of the nematodes and trematodes by their circular outline and, as a rule, by their smaller size.

The eggs of *T. saginata* and *T. solium*, which are indistinguishable from one another, are provided with a single brown striated outer membrane, which encloses a ciliated six-hooked onchosphere (Plate XXVII, 16, 17). On the other hand, *Hymenolepis nana* eggs (40 μ) have two transparent membranes (Plate XXVII, 20). Individual eggs of *T. saginata* are more ovoid than those of *T. solium*, and measure 30 μ in diameter. Eggs of *Diphyllobothrium latum* (70 μ by 45 μ) are translucent, oval and provided with an operculum (Plate XXVII, 21).

A simple method of counting hookworm eggs (Wilkins).—A thick slide, 75 mm. by 25 mm. by 1.7 mm., is cut into three equal pieces. The two end portions are cemented with *Durofix* to the ends of another slide, leaving a space about 25 mm. square, over which another slide about 20 mm. long is eventually laid, enclosing a space of more than 1 ml. capacity. A 1 ml. pipette, graduated in hundredths, is cut into five short lengths, each containing 0.2 ml. Then, a piece of galvanized wire, which will fit the bore of the pipette, is cut into pieces 4 mm. long, one end of each being bent over in the form of a handle, and the other end being filed off square.

The stool is stabbed with a piece of pipette until this is filled to the 0.1 ml. mark. It is pressed down and twisted, the excess being wiped off. The fæces are pushed out with a piece of wire on to the prepared slide with 0.9 ml. of saturated salt solution. Glycerine is then added slowly from a heated graduated pipette ; the fæcal emulsion is covered with the top slide and put aside for 30 mins. to permit eggs to float up. All eggs in the area covered by the emulsion are counted. The result, multiplied by 10, gives the number of eggs in each ml. of stool.

Methods of concentrating helminth eggs.—Clayton Lane devised a technique, known as the "flotation method," which is accurate and useful in the mass diagnosis of ancylostome and, to a certain extent, of other helminth infections. The eggs are collected from 1 ml. of fæces by "direct centrifugal flotation." The aim of the apparatus is to keep fixed upon the centrifuge tube a square glass cover which will collect the floating eggs, and which is held in place by a cover-slip of such a shape as to prevent movement and leakage, and yet permit

ready removal of the cover for direct microscopical examination, thus making the area of collection and examination identical. (Fig. 457.) The centrifuge tube is a glass cylinder, $4\frac{1}{2}$ in. long by $\frac{1}{2}$ in. in internal diameter, closed at the bottom, and with the mouth ground off flat at right angles to the long axis of the tube. The cover is held in position during centrifuging by a cover-slip. The centrifuge is fitted with an axial *tachometer*, which records the speed at which the instrument is being revolved. The centrifuge tube is suspended in a metal bucket of $1\frac{1}{2}$ in. internal diameter. Two such buckets are employed, each containing a centrifuge tube, fitted at the upper ends with metal prongs which hold the glass overslips in position. Faeces (1 ml.) are first disintegrated by vigorous shaking in water in a closed tube, and centrifuged for one minute

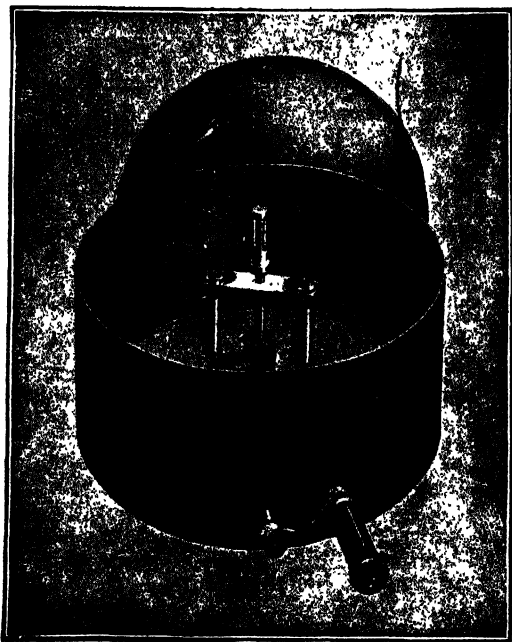


Fig. 457.—Clayton Lane's centrifuge. *Greatly reduced.*
(As supplied by Messrs. R. B. Turner & Co.)

at 1,000 revolutions; the supernatant fluid is decanted, and a solution of salt of a specific gravity of 1.150 added, and centrifuging is repeated for thirty seconds at 1,000 revolutions; the tube should be filled so that the saline lies in contact with the under-surface of the cover-clip. The eggs adhere to the under-surface of the glass, which is carefully removed and examined as a "hanging-drop" preparation.

Direct centrifugal flotation gives a greater and more reliable concentration than any other method; the examination area is about $\frac{1}{2}$ sq. in., and the whole process is carried through in a few minutes.

Zinc sulphate centrifugal flotation for concentration of helminthic ova and protozoan cysts (Faust's method, modified by Watson).—For this method, which is highly recommended, the following technique is employed:—A sample of stool, the size of a pea, is placed in a glass centrifuge-tube and broken up to

form a fine suspension in distilled water. It is then centrifuged for three minutes at 1,500 revolutions per minute, using an ordinary laboratory centrifuge with a radius of $5\frac{1}{2}$ in. Supernatant fluid is then removed and the process repeated until it is clear. Zinc sulphate solution (33 per cent., sp.G. 1.18) is poured into the tube and the packed sediment is broken up into a uniform suspension. Then a chemically clean circular cover-slip, of slightly greater diameter than the glass tube, is smeared on one side with a thin film of Mayer's egg medium (white of egg 50 ml., 50 ml. glycerine, salicylate of soda 1 grm., shaken well together and filtered) and pressed firmly on top of centrifuge tube. The suspension is again centrifuged for three minutes at 1,500 revolutions per minute. The cover-slip is carefully lifted off the top of the tube and placed, prepared-surface downwards, on a drop of Weigert's iodine solution on a slide.

Simple flotation method (Hung).—Two grammes of fæces are carefully rubbed up with a glass rod and saturated salt-solution; the mixture is poured into a watch-glass or wide tube, which is filled to the brim. A slide, or cover glass, is placed in contact with the fluid and allowed to remain for ten minutes. When ancylostome eggs are present they will be found adhering to the under-surface of the slide or cover-glass.

Aex method (Faust's method simplified).—In the Aex method of Loughton and Stoll 56 ml. of tap water are placed in a Stoll flask and 4 ml. of fæces, emulsified in water, added. The whole is vigorously shaken with glass beads to produce a homogeneous product. 1.5 ml. of this is placed in a 15-ml. centrifuge tube and to this are added 3.5 ml. of 20 per cent. hydrochloric acid. After stopping with a rubber plug the mixture is shaken for one minute then put aside. Next 5 ml. of a mixture of ether and xylol in equal parts are added and the whole is again shaken for one minute and centrifuged at 1,800–2,000 r.p.m. for two minutes. The material collected on the walls of the tube is carefully removed by a thin piece of wood, the supernatant fluid is poured off and one drop decinormal NaOH added to the deposit. Some of this is removed by a capillary tube and examined. This method is best for *Ancylostoma*, *Trichuris* and *Ascaris* eggs and for *Strongyloides stercoralis*.

Fülleborn's method for detection of schistosome eggs in the fæces.—The diagnosis of intestinal schistosomiasis (*S. mansoni* and *S. japonicum*) by detection of the eggs in the fæces is not always easy. Fæces of the volume of a hazel-nut are placed in a conical glass, carefully rubbed up with a glass rod and a little 2½ per cent salt-solution, and put away to settle, in the dark, for five minutes. The solution is poured off from the sediment, and the process repeated two or three times.

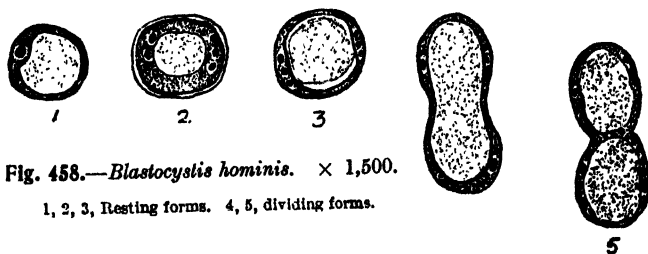


Fig. 458.—*Blastocystis hominis*. $\times 1,500$.

1, 2, 3, Resting forms. 4, 5, Dividing forms.

The schistosome eggs remain in the sediment, which is flooded with distilled water at 120° F. and exposed to a bright light.

The miracidia now escape from the eggs, and can easily be detected with a hand lens, particularly against a dark background. On adding a few drops of perchloride of mercury solution, they are killed off and are found in the sediment.

Benzidine reaction for blood pigments.—Required (1) Benzidine, (2) Sodium perborate. Tablets obtainable of 0.1 gm. each glacial acetic acid.

Procedure.—Grind one of the tablets and dissolve in 5 cc. of glacial acetic acid and 5 cc. of water. Filter—place 2 drops of filtrate on a clean slide. To one of the drops add a platinum loop of the material to be tested. If blood is present a green colour appears in less than one minute.

Occult blood.—1 ml. blood gives a positive reaction with most methods in simple, infective or malignant ulceration anywhere in the bowel (including the

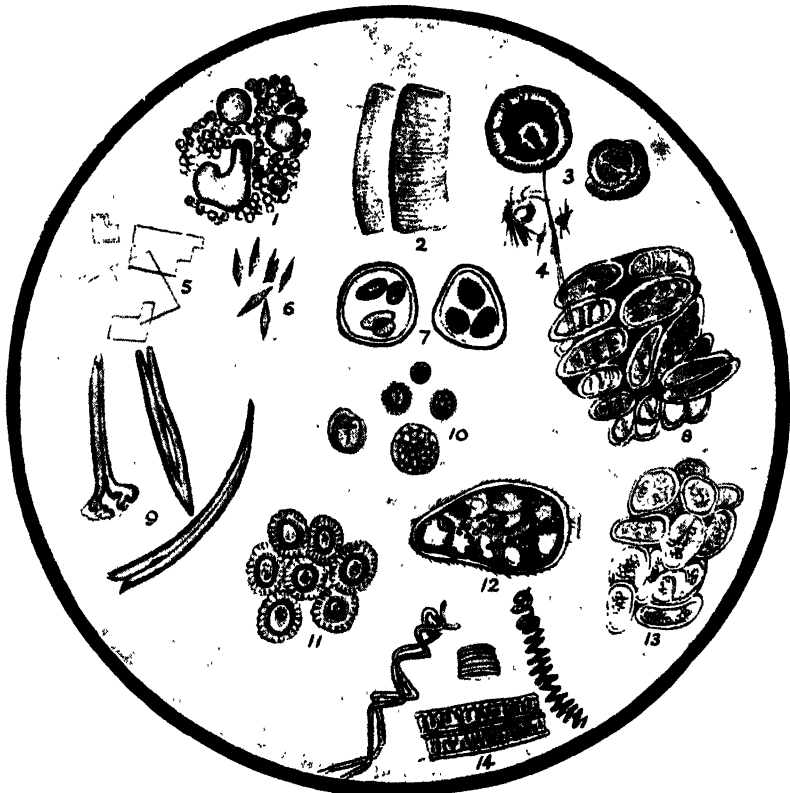


Fig. 459.—Microscopic appearance of common objects in the fæces.
× 800 diam.

1, Casein and fat droplets; 2, muscle-fibres; 3, soap crystals; 4, crystalline fatty needles; 5, cholesterol crystals; 6, Charcot-Leyden crystals; 7, truffle spores; 8, portions of husks of cereals; 9, hairs of wheat grain; 10, spores of fungi; 11, cells from pericarp of peas; 12, parenchyma of beans; 13, endosperm of rice; 14, vegetable spirals.

pharynx) particularly hiatus hernia, peptic ulcer, duodenal ulcer, œsophageal varices, carcinoma of stomach, carcinoma of colon, piles, some worm infections—ancylostomiasis, schistosomiasis—amœbic dysentery, purpura and many bleeding and clotting diseases. False positives may be caused by ingestion of much green and vegetable matter, meat, or liver. Unless the test is strongly positive, positive results must be checked by repeating the test after a few days on "occult blood diet."

Microscopical examination and recognition of various elements in the fæces.—*Blastocystis hominis* (Fig. 458).—Sometimes during examination of fæces, a yeast-like organism—*Blastocystis*—simulating an amoebic cyst, but less refractile, is encountered. (Plates XXIV, XXV.) Each cell contains a large central vacuole, while the cytoplasm is reduced to a thin layer in which are situated one or two small iodophilic nuclei at each pole. The cytoplasm contains refractile globules of *volutin* which should not be mistaken for the nuclei. *Blastocystis* multiplies by gemmation and rapidly increases in culture media such as are suitable for *E. histolytica*, unless dextrose has been added. The organism varies a good deal in size and shape; single cysts measure from 5–20 μ in diameter. This organism has no pathogenic significance.

Muscle-fibres, derived from meat, practically always occur in the stools, and are recognized by their cross-striation. When present in large numbers they indicate defective intestinal digestion. (Fig. 459, 2.)

Connective tissue, derived from meat, somewhat resembles mucus; it is distinguished by striation, which disappears on addition of acetic acid. When it is present in large masses, defective gastric digestion may be inferred. Elastic fibres have no significance.

Starch granules, derived from fruit and potatoes, are stained blue by iodine solution. They vary in size and shape, according to the food from which they are derived. Well-preserved granules with concentric markings are seldom seen. They are often enclosed in a cellulose covering, and can readily be recognized, except those from peas and beans, which roughly resemble tapeworm eggs.

Excess of starch is pathological, and such a stool is usually acid and shows signs of gas-bubbles, fermentation, and yeasts. The iodine test may be applied to ascertain the extent to which starch has been digested. A blue colour indicates unchanged granules: red, that digestion has begun.

Detritus derived from fruits and vegetables is easily recognized by spiral ducts, areolar tissue, vascular bundles and pigment cells.

Neutral fats, derived from fat, are recognized as colourless, highly refractile droplets, or sometimes as irregular bile-stained masses which are stained by Sudan III and are insoluble.

Fatty acids, derived from fat, occur as sheaves of colourless acicular crystals, which melt on being warmed and dissolve in ether. (Fig. 459, 4.)

Soaps from the fat of food occur as greasy-looking amorphous masses, or sometimes as needles, which are thicker and not so long as those of the fatty acids. They may be colourless, or stained with bile-pigments. Insoluble in ether, as are fatty acids, they do not melt on being warmed. If the film of fæces on a slide is treated with acetic acid and heated fatty acid crystals will separate out. (Fig. 459, 3.)

Fats may be distinguished from mucus or from vegetable material by the following rough test: prepare a smear of the stool on a slide, put on a cover-slip, and press the latter down on to the smear: should the material be of fatty composition, the cover-slip will remain in place; if vegetable detritus or mucus, it will spring back when pressure is released. (Fig. 459, 1.)

In a normal stool, fat is present almost entirely in the form of amorphous masses of soap, less often as crystals. Neutral fat is normally absent.

Mucus occurs as transparent shreds, sometimes bile-stained. It has always a pathological significance and, when it contains leucocytes and epithelial cells, indicates intestinal ulceration.

Intestinal sand.—Sand grains in the fæces of persons who live in deserts are extremely frequent, but sand-like material is a pathological product sometimes present in diverticulitis.

Charcot-Leyden crystals are frequently found in stools containing *Entamoeba histolytica* (Fig. 459, 6). These crystals have a chemical connection with eosinophil cells; they are therefore most evident in diseases with an eosinophilia. Originally seen in leukæmic blood, they are recorded in smear preparations from periarthritis nodosa, trichiniasis, intestinal infections, and in localized collections of eosinophils in nasal polypi and skin blebs.

Pseudo-parasites.—It frequently happens that orange-pulp is mistaken for trematodes, banana fibres for small tapeworms, pieces of cotton-thread and celery for *Enterobius vermicularis*, *Ancylostoma duodenale*, etc. In microscopic diagnosis numerous objects may be mistaken for helminthic eggs, and it is important that the tropical worker should be able to recognize various articles of diet as they appear in the stools. The spores of *Trichosporium* which occasionally are seen in the fæces, may be mistaken for eggs of *Ascaris lumbricoides*, owing to their size (42–86 μ) and rough surface. (Fig. 459, 7.) The spores of mushrooms have a somewhat similar appearance. Pollen grains of plants and spores of fungi have given rise to difficulties, in spite of their characteristic appearance; pollen of conifers is often met in the stools of people living near pine forests. All these spores are globes with a reticulated surface which can be made out on careful focusing. (Fig. 459, 10.) Occasionally cheese-mites and their eggs may be seen in the fæces.

Demonstration of protozoa in fæces.—It is difficult to make out the nuclear details of the intestinal protozoa and their cysts in a fresh state. Weigert's iodine solution (iodine, 1 part, pot. iod., 2 parts, water, 100 parts), which has a special affinity for nuclear structure, renders the details much more evident, and assists in their recognition. (Plate XXV.)

Technique for differentiating and preserving protozoa in fæces.—(Buck, Wells and Vail.) Two grm. of brilliant cresyl blue, dissolved in 75 ml. methamil, are added to 5 ml. formalin, 2.5 ml. liquid phenol and 15 ml. distilled water. A small portion of fæces is well mixed with a large drop of this solution on a slide and the preparation examined under a cover slip.

Trophozoites of amoeba are fixed with pseudopodia extruded and ingested red blood corpuscles stained black. Nuclei become distinct: chromatoid bodies stain blue and glycogen remains unstained.

Penetration of this reagent into cysts is extremely rapid. Flagellates and amoebæ may be diagnosed which gives pictures as satisfactory as those stained by iron hæmatoxylin. (See also Kohn's Method, p. 1094.)

Methods of concentration of protozoal cysts in fæces.—Yorke advocated the following method of concentration, especially applicable for cysts of *Entamoeba histolytica*:

A mass of fæces is ground up with water in a small mortar and the emulsion shaken with 500–1,000 ml. of water, poured into a tall glass cylinder, and allowed to stand for fifteen minutes, to permit the coarser faecal material to settle. The supernatant fluid is withdrawn and centrifuged, and the deposit is shaken up with a solution of cane-sugar of specific gravity of 1.080 and again centrifuged quickly. This procedure results in the separation of cysts from the remaining faecal material. The fæces are precipitated and the cysts left floating in the supernatant fluid, which is withdrawn, diluted with about four times its volume of water, and again centrifuged at high speed. By these means a small deposit is obtained, consisting of great numbers of cysts in a relatively minute quantity

of faecal material. The deposit is then washed several times with water to get rid of all traces of sugar and the majority of the remaining bacteria.

An efficient and practical method is that of Ridley and Hawgood (1956) which ensures a concentration of 20-30 times. 1-2 grm. of faeces are emulsified in 10 ml. of 10 per cent. formol saline. It is put through a 40 mesh sieve into a centrifuge tube, and 3 ml. ether are added, and it is then shaken vigorously. The centrifuge is regulated so that 2,000 r.p.m. are reached after two minutes. The fatty debris is loosened with a swab stick, and the supernatant fluid is decanted. The small deposit left at the bottom of the tube is then examined for cysts.

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